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Cardiovascular Risk Assessment in Diabetes and Chronic Kidney Diseases: A New Insight and Emerging Strategies

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1. Introduction

The post-millennium era witnesses a substantial epidemiologic transition in which cardiovascular disease (CVD) has taken more important role in mortality and morbidity in almost all parts of the world[1]. However, the natural history of CVD itself has also been evolving in parallel to changing life style and environmental risk factors. Nevertheless, despite a global movement for CVD control, the target points are still poorly achieved[2]. Therefore, a new look at the issue of CVD pathophysiology, CVD markers and risk assessment is necessary for a proper and effective care plan and targeting CVD prevention and control.

The classification of some elements to "*risk factors*" and "*risk markers*" has been controversial. There have been serious debates about the validity and impact of classic CVD risk factors. However, it is generally accepted that classic CVD risk factors cannot fully explain the epidemiology and natural history of the disease particularly in patients with co-morbidities. As a result several lists of emerging risk factors have been introduced with various clinical or research applications. Accordingly, several risk scores have been developed for risk assessment among various populations. Nevertheless, we face a network of associated risk factors with synergic effects, of which some factors play central roles and connect other factors together. For instance, central arterial pressure and arterial stiffness and also microalbuminuria have attracted more attention as summative CVD markers or risk factors and have been proposed as new targets for more efficient treatment.

Increasing evidence of cross-links among CVD, diabetes mellitus (DM) and chronic kidney disease (CKD) has been published in recent decades. DM and CKD are major comorbidities with CVD. In addition, several studies demonstrated greater frequency of CVD in DM and CKD, even in very early stages. On the other hand, our recent research revealed a significant impact of minimal heart dysfunction on further development of renal impairment[3]. Then, it seems that CVD, CKD and DM shares many risk factors and influences each other in various stages. This could be demonstrated as a pyramid with facets of presentations and a common pathophysiologic base. Considering this network of associations, we have introduced the concept of *circulatory (MARC) syndrome*, which facilitates understanding, evaluation, detection and interventions on the CVD risk factors earlier, easier and more effective. This concept preserves the positive features of the so called "*metabolic syndrome*"

but prevents its weaknesses and improves its clinical applications. This leads to a novel paradigm in CVD management with new checking points, new targets and better achievements in the patients' care.

2. Epidemiologic trends in CVD risk factors

CVD has been evolving through 4 epidemiologic transition periods[1] with increasing frequency of proportion of death due to CVD during the first 3 stages and a slight decrease in the disease rate in the 4th stage, possibly due to controlling CV risk factors. However, it seems that a 5th stage is being developed due to epidemic diabetes, hypertension, obesity and chronic kidney disease as well as leveling off the smoking session rate in combination to social and economic instability in many countries. Consequently, epidemiologic trends in CVD and CV risk factors have been changing during the past decades both in developed and in developing countries. Developing countries, in particular, experience a substantial rise in CVD and younger age at onset of the disease, which is partially attributed to their demographic remodeling including a high population growth rate and inverted population pyramid with a majority of young individuals [1]. Furthermore, these countries face to a "dual epidemiology" of contrasting an undernourished and poor population against a significant proportion of overweight and obese groups. The last World Health Organization report on global burden of disease and risk factors demonstrated that the highest rates of CV death were in Eastern Europe, Central Asia, Middle East and North Africa. Also six out of 10 countries with highest rate of diabetes were in Eastern Mediterranean and Middle East region. However, there was a considerable heterogeneity in other regions which reflects different stages of epidemiologic transitions even in a single country like China[1, 4].

Eight risk factors (alcohol use, tobacco use, high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake, and physical inactivity) account for 61% of cardiovascular deaths[4]. Moreover, air pollution, climate change, psychosocial stressors and maternal-foetal metabolic adaptation are also introduced as important CV risk factors[1]. However the pattern of the risk factors differs in subgroups of age, gender and patient groups while some factors loses their impact in parallel to homogeneity of the factor in the group[5]. It also evolves as a population passes through epidemiologic transitions from traditional to emerging risk factors.

From a practical perspective, primary and secondary prevention must be arranged for modifiable risk factors. The Framingham Study and subsequently the INTERHEART study have identified the important risk factors and targets for modification. Moreover, an analysis of 10 studies across the world in which there has been a decline in CVD mortality, demonstrated that risk factor modification was associated with 44% of the decline in the Netherlands, 50–54% in the USA, and 76% in North Karelia, Finland. New treatments are responsible for 23–47% of the decline in mortality[1]. Although, economic, cultural and logistic conditions have various impacts on preventive strategies in different population; *risk assessment* is a fundamental step for any CV preventive strategy.

2.1 CV risk in diabetes mellitus

CVD is the leading cause of mortality among DM patients [6, 7] with the prevalence of, incidence of, and mortality from all forms of CVD being 2-8 fold higher in diabetics when

compared to a non-diabetic population. DM is accompanied with various cardiovascular abnormalities including endothelial dysfunction, increased oxidative stress and micro- and macrovascular consequences leading to coronary artery disease, left ventricular dysfunction (particularly diastolic dysfunction), hypertensive heart disease and reduced cardiac reserve[8]. A different trend in CV risk factors has been reported in patients with and without DM in Framingham Study from 1970 to 2005. This study demonstrated a greater increase in BMI, greater decrease in cholesterol and similar reduction in hypertension in DM when compared to non-DM[2].

The special writing group for the *American Heart Association* established that the goal of risk assessment would be to identify subclinical CVD in patients with DM which would lead to better management and improvement in disease morbidity and mortality. Furthermore they also designated DM as a “coronary risk equivalent” and indicated that DM patients belong in the same risk category as patients with known CVD[9]. This risk increases with age (>35 yrs), younger age at onset of DM, duration of DM (>10 yrs), presence of microvascular complications and other CV risk factors [10, 11]. Screening and CV risk assessment of DM patients is also strongly recommended in many guidelines including a French guideline which recommended screening for silent myocardial ischemia (including exercise stress testing) in DM patients with one additional risk factor [9]. However, the *American Heart Association* recommended exercise testing in this group when individuals plan moderate to high intensity exercise[11]. Furthermore, while the hemodynamic response to increased physical activity is a predictor of future hypertension [12] and is helpful in the early diagnosis of heart failure[13], it might also provide further information about the factors contributing to impaired cardiovascular control even in DM patients without additional risk. Accordingly, we demonstrated in a study of more than 17000 patients (including 1722 DM pts) an impaired hemodynamic response to exercise stress testing in DM group compared to non-diabetics and most importantly showed that the responses predicts the development of ESRD in diabetic patients[3, 14-16]. (Figure 1) Furthermore, in an outpatient setting of patients with diabetes and hypertension; we reported a substantial proportion of patients being non-dipper for nocturnal blood pressure. This study also showed an inverse relationship between white coat hypertension and arterial stiffness or microalbuminuria[17]. A comparison between normal individuals, patients with impaired fasting glucose, and diabetic patients did also demonstrate an increment of arterial stiffness in these groups[18]. In conclusion, all above evidence indicate subclinical arterial changes early in DM.

2.2 CV risk in diabetic kidney disease

About 10-40% of patients with diabetes mellitus (DM) develop nephropathy. Consequently with an increasing DM global prevalence and an aging population, DM has become the leading single cause of ESRD in many developed and developing countries [19-24]. Moreover, it is now proven that even a mild reduction in kidney function is accompanied by an increased cardiovascular (CV) risk [25, 26]. In addition, cardiac and renal DM complications share many risk factors and markers including microalbuminuria (mA), atherosclerosis and arteriosclerosis [27-29]. Therefore, evaluation and treatment of renal risk factors should not only prevent progression to End-Stage Renal Disease (ESRD), but also reduce CV risk.

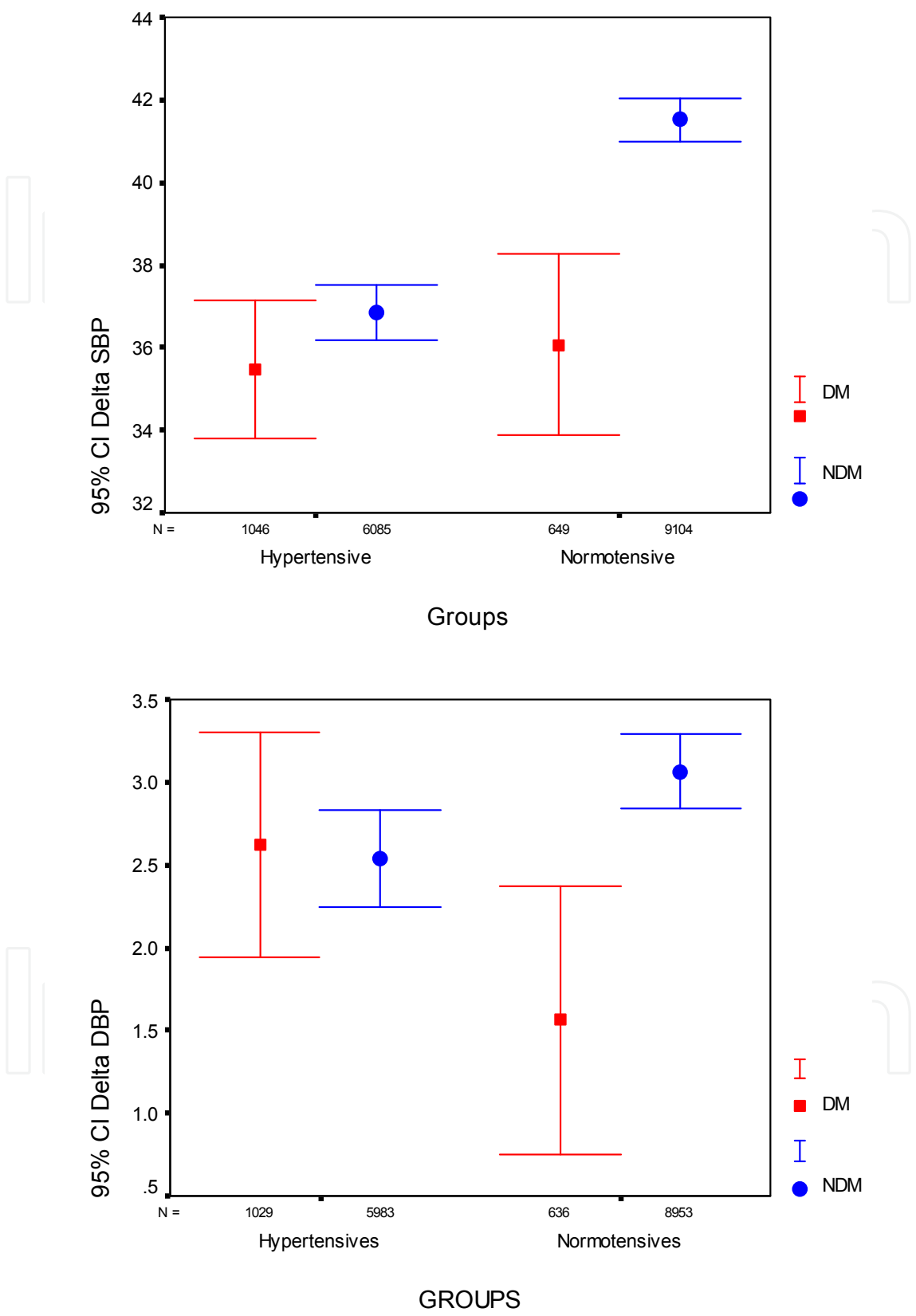


Fig. 1. Differential response of DM and NDM to the exercise test in hypertensive and normotensive subgroups

While the development and progression of renal damage in DM occurs very slowly, it often remains subclinical and undiagnosed for years [30], which inhibits effective prevention and intervention at a time when renal damage may be reversible. Therefore, early identification of diabetic nephropathy (DN) is a medical priority [31, 32]. Although mA is currently regarded as an early marker of DN, it is now preferably considered as a marker of a generalized endotheliopathy and then a CV risk marker. However, irreversible damage has often occurred when mA is detected [30, 33]. Furthermore, mA may not accurately represent the severity of renal damage, absent in marked renal dysfunction [34, 35] or may regress or fluctuate during the disease [34, 36]. Consequently, other markers, preferably in their early stages, should also be investigated as a potential guide to the progression of ESRD [31]. Arterial compliance changes occur early in DM and since arterial stiffness is an established independent predictor of mortality in the later stages of nephropathy [37-39], it should also correlate with renal function and BP profile in the earlier stages of DM.

Based on the above understanding, we made a large study including several subsets with various range of kidney function and compared CV risk factors in DM and non-DM, focusing on early stages in particular. The findings indicated that even in early stages of renal impairment without clinical presentation, DM patients had a greater level of arterial stiffness compared to non-DM. As a result, indices of arterial stiffness could be applied for a better CV risk management particularly in DM[40]. (Figure2). Multivariant analysis revealed arterial stiffness, hemoglobin, systolic blood pressure and triglyceride as the main determinants of renal function in DM (Table 1). Application of artificial neural network for analysis of major predictors of kidney function also determined arterial stiffness, hemoglobin, triglyceride, diabetes and blood pressure profile among major determinants of renal function.

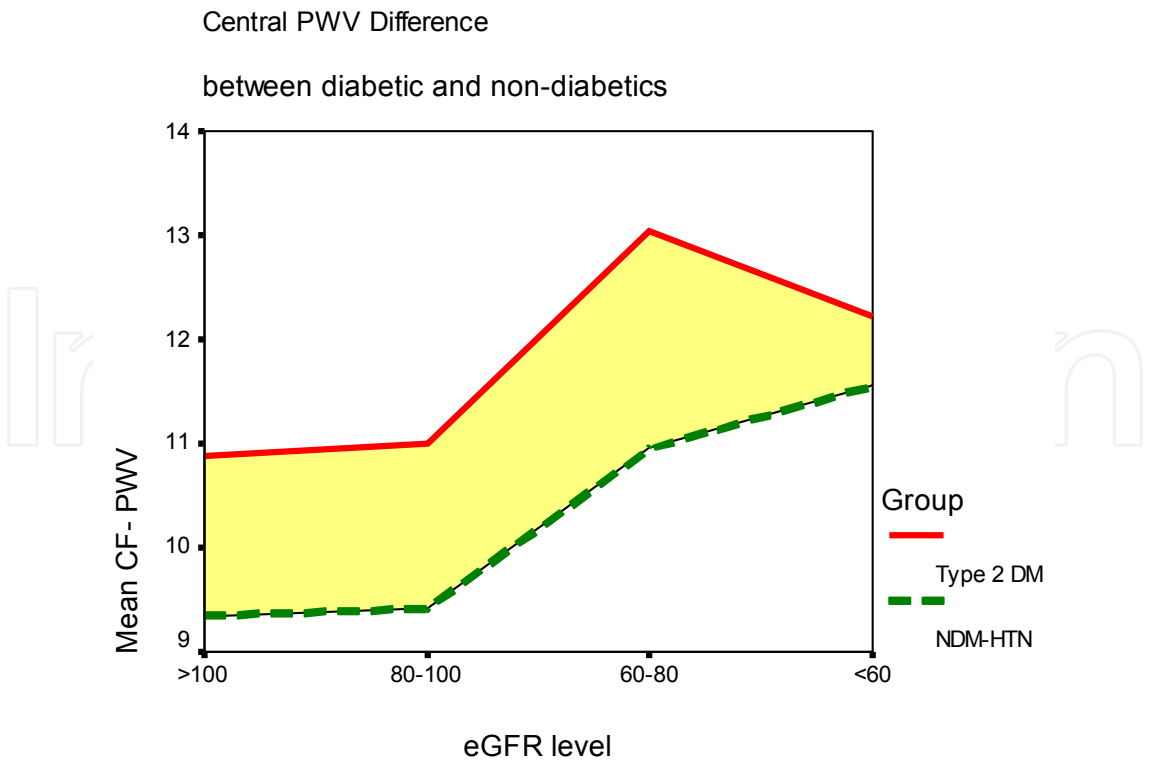


Fig. 2. Difference in the central arterial stiffness (as measured with CF-PWV) between type 2DM and NDM groups across levels of eGFR

Adj.R ²	Model 1 48%	Model 2 49%	Model 3 50%	Model 4 51%	Model 5 52%	Model 6 52%	Model 7 53%	Model 8 52%
rTr	0.397 0.259	0.403 0.245	0.393 0.249	0.411 0.222	0.410 0.219	0.202 0.116	0.202 0.115	0.298 0.009
Male Gender	-0.279 0.038	-0.278 0.036	-0.263 0.033	-0.282 0.015	-0.288 0.012	-0.275 0.014	-0.269 0.015	-0.281 0.012
CV disease	-0.273 0.040	-0.275 0.037	-0.269 0.037	-0.287 0.018	-0.280 0.020	-0.283 0.018	-0.282 0.017	-0.277 0.021
Hb	0.352 0.010	0.342 0.009	0.329 0.008	0.351 0.002	0.351 0.002	0.356 0.002	0.355 0.001	0.361 0.001
HbA1c	-0.152 0.217	-0.163 0.161	-0.153 0.168	-0.158 0.150	-0.155 0.154	-0.149 0.165	-0.164 0.122	-0.186 0.082
TG	-0.304 0.014	-0.294 0.013	-0.287 0.013	-0.293 0.010	-0.288 0.010	-0.299 0.007	-0.300 0.006	-0.273 0.012
Peripheral DBP	0.087 0.597	0.101 0.516	0.129 0.323	0.149 0.225	0.148 0.222	0.158 0.187	0.173 0.142	
ACE-I	0.099 0.396	0.105 0.354	0.109 0.328	0.094 0.372	0.089 0.394	0.079 0.440		
HR	-0.199 0.540	-0.207 0.517	-0.207 0.513	-0.207 0.508	-0.211 0.496			
ARB	0.057 0.597	0.056 0.598	0.065 0.532	0.062 0.541				
Age	-0.075 0.635	-0.071 0.649	-0.072 0.642					
Peripheral SBP	0.060 0.689	0.048 0.739						
Insulin	-0.040 0.748							

Table 1. Regression models for determinants of eGFR in the DM group, Values are β (upper line) and P value (lower line)

2.3 CV risk in ESRD

Cardiovascular disease (CVD) is a common complication in end-stage renal disease (ESRD) with a 10 to 30 times greater CVD mortality compared to the general population[41]. Traditional CV risk factors while more prevalent, cannot fully explain this increased CV event rate in ESRD[28] and other factors including increased lipoprotein-a (lipo-a), adipokines, asymmetric dimethylarginine (ADMA), hyperhomocysteinemia, hyperparathyroidism and arterial stiffness have been implicated [27, 42-46]. In turn, arterial stiffness is affected by several hemodynamic and metabolic factors.

Diabetes mellitus (DM) is the leading cause of ESRD [43]. It is also a major CV risk. Despite medications and attempts to control these CV risk factors, CV events still remain the most

common cause of mortality both in DM and in ESRD [47-49]. While a greater risk of CV events is expected in DM compared to non-DM patients with ESRD, the available reports regarding the risk profile in DM and non-DM patients with ESRD are conflicting [42, 43, 50-53]. Likewise interactions between ESRD and DM in the development and progression of arterial stiffness are not completely clear [54, 55]. As a result of several metabolic factors which contribute in arterial stiffening, vascular calcification is proposed as the fundamental phenomena in arterial stiffness and is certainly a frequent finding in ESRD and DM [56-58]. However the mechanisms for the development of vascular calcification are not completely understood. In particular, reports of its relationship with calcium homeostatic mechanisms including parathyroid hormone (PTH), phosphate and the calcium-phosphate product ($\text{Ca} \times \text{P}$) and vitamin D are inconsistent [58-62].

In an attempt to clarify classic and emerging risk factors in ESRD, we conducted a study of 100 diabetic and non-diabetic (paired matched for age and gender) individuals with ESRD and demonstrated blood pressure, heart rate, height and renal function as well as metabolic profiles, including cholesterol, homocystein, lipo(a) and CRP were comparable. However, carotid-femoral PWV (12.3 ± 0.5 vs 10.3 ± 0.2 ; $P < 0.001$) and pulse pressure (71.2 ± 2.2 vs 64.2 ± 2.4) were significantly greater in the DM group, despite a comparable A1c and waveform reflection time. Multivariate analysis demonstrated PTH to be a significant PWV determinant after adjustment for DM, renal function and BP ($P = 0.038$). As a particular novel finding, calcium-phosphate product had a u-shape association with central and peripheral PWV ($P < 0.05$), that is both low and high levels of calcium-phosphate product increases the CV risk in this group which was similar to its relationship with mortality, reported by Block et al. In conclusion, arterial stiffness as an established, independent and strong predictor of mortality in ESRD patients [63, 64] is possibly the factor that links cardiac and renal disease (Figure 3) [25]. Consequently, we proposed a model that can explain association of the factors (Figure 4).

2.4 CV risk in kidney transplanted patients

Kidney transplant patients have a lower risk of CVD compared to dialysis patients, even after controlling important source of selection bias including age [65]. However, CVD is still a common cause of post-transplant death [19]. Nevertheless, classic risk factors cannot fully explain the CV risk in this population. It is reported that the Framingham CV risk score significantly underestimates the risk of ischemic heart disease in transplant patients [66] and therefore, non-classic risk factors including C-reactive protein, homocystein and renal function as well as arterial stiffness may contribute in CV risk in this population [67, 68].

In support to the previously demonstrated findings our group studied 100 kidney transplanted patients (including 33 DM) and reported with a comparable classic CV risk factors, homocystein and renal function had a greater arterial stiffness when compared to non-DM. Also an improvement in central arterial stiffness was observed after a year of follow-up [69, 70]. This is in line with the other evidence that cardiac function in DM transplant candidates is carefully evaluated prior to transplantation and LV systolic, diastolic function and arterial compliance improves shortly after a successful renal transplant [71-75]. It was also concluded that assessment of arterial stiffness may improve pre-transplantation risk assessment both in donors and recipients [70].

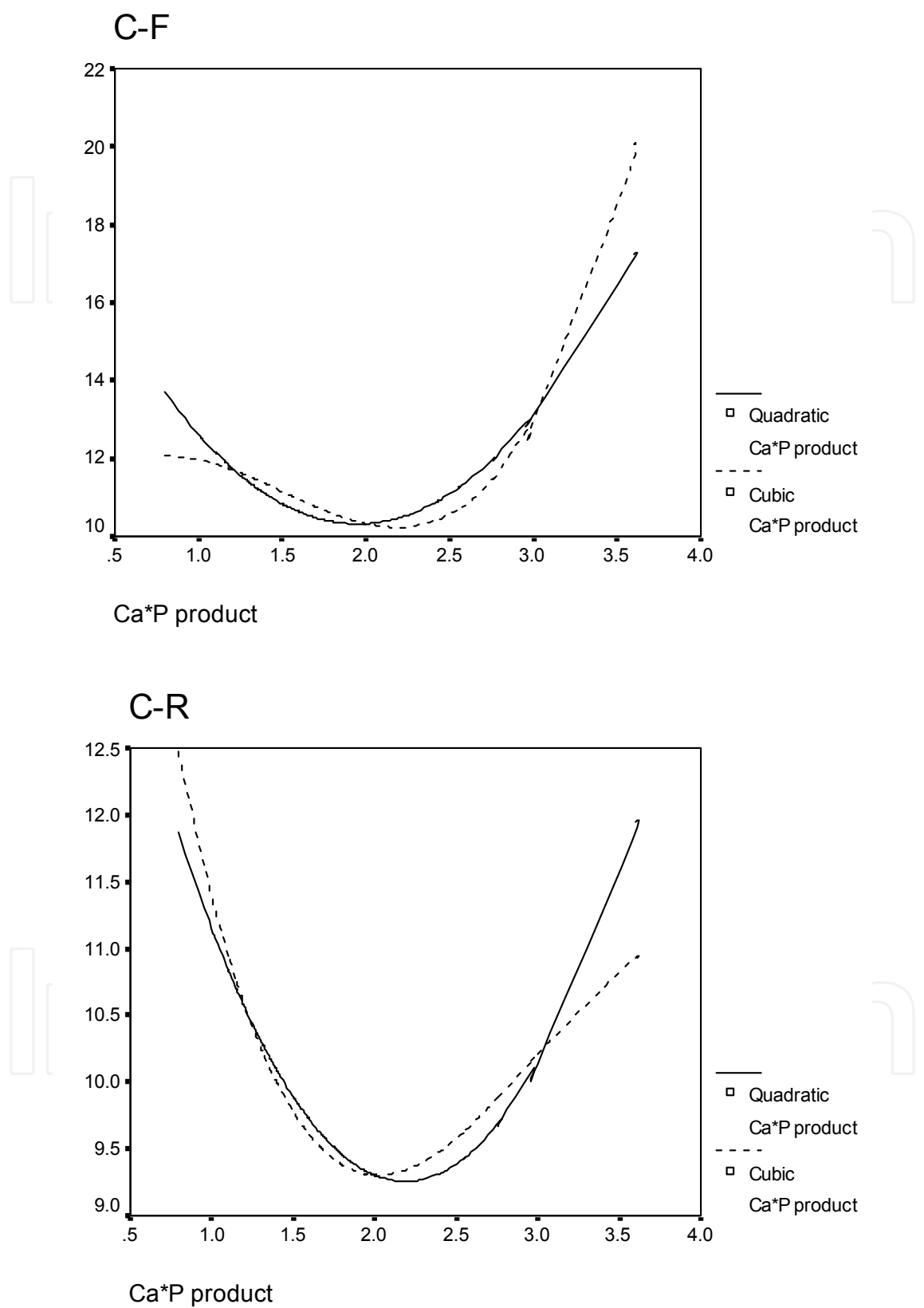


Fig. 3. Non-linear relationship between central (left) and peripheral (right) pulse wave velocity with calcium-phosphorus product in ESRD

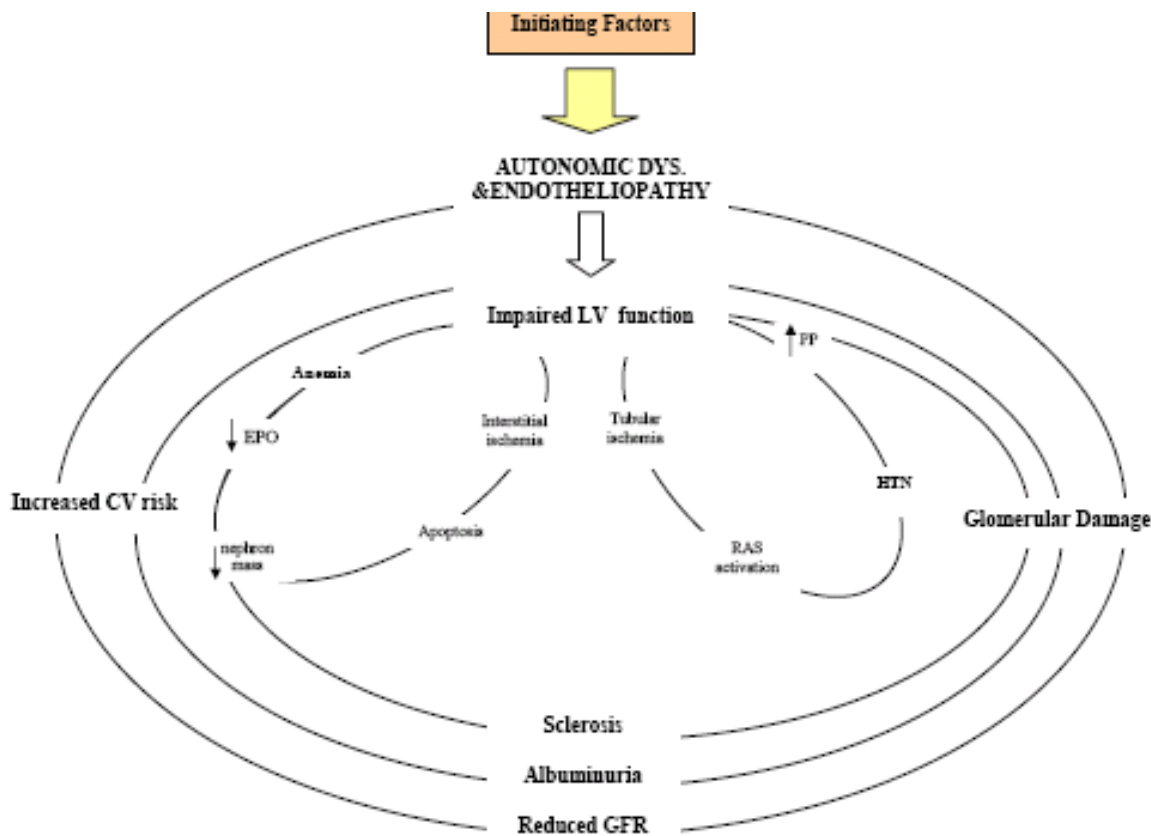


Fig. 4. Hypothetical model for explaining Renal-Cardiac Cross talk

3. Fundamentals in CVD risk assessment

The global epidemic of diabetes and chronic kidney diseases and their effect on the increased incidence of CVD, stresses on undeniable requirement for a timely effective CVD risk assessment in order to implement prevention strategies.

Risk assessment is a fundamental component of primary and secondary preventive strategies and an important skill in clinical epidemiology in particular for chronic diseases such as diabetes mellitus (DM) with potentially preventable multi-organ involvement. Although many risk factors have been identified as promoting DM complications, the presence of a risk factor only demonstrates the “risk” or the “possibility” of the given outcome since not all patients with the factor develop an adverse outcome and vice versa. However from a preventive point of view the medical approach is the attempted reduction of all risks factors so as to decrease this possibility. Nevertheless, decision thresholds are important determinants of risk factor management.

Traditionally, patients are assessed and managed based on the presence or absence of individual risk factors with a target point for each risk factor being determined and medical interventions (commonly by separate specialties) applied to achieve these targets. However, these risk factors also interact and can augment or diminish each others effect. In other words, patients with a particular risk factor might be more prone or more susceptible to be influenced by another risk factor. Moreover risk factors may have a *synergistic effect* thereby producing a greater impact beyond a summation of their individual risk. Accordingly, different target points have been assigned for various patient subgroups. For instance,

recent practice guidelines suggested different target blood pressures for DM patients with and without proteinuria [76, 77]. Nevertheless, most risk factors such as BP have a linear relationship with the adverse outcome (i.e. CV events or mortality), even when levels are below the arbitrarily defined cut-off points [78, 79]. In an attempt to overcome this problem, new definitions such as pre-hypertension, pre-DM and pre-microalbuminuria have been added to recent practice guidelines [76, 77, 80], although they may have enhanced uncertainty and confusion rather than improve patient care.

While the target point approach appears to be straightforward, there may be a substantial risk of unnecessary treatment or neglect when treating certain patients. Consequently, a *multifactorial risk assessment* approach whereby a planned therapy is based on an individual's absolute risk is now encouraged [81]. This multidisciplinary approach is expected to be more effective, both medically and economically.

The simplest way to estimate a multifactorial global risk is to use the number of the present risk factors. For instance the number of present components of the metabolic syndrome associated with the risk of CV disease in DM or the development of renal impairment [82, 83]. Alternatively, each factor can be graded in an individual patient and scored (e.g. using the GCS in comatose diabetic patients) and then the total score is considered as representative of the severity of the condition and predictive for the outcome [84]. A more scientific approach would be to sort the factors according to their importance or the strength of their association and calculate a total risk or a "risk score" by summation of the weighted utilities of the factors. The appointed weight could be based on expert opinion or better still on more objective criteria. This technique should simulate the medical decision making process by a medical practitioner where the better the weighting the more accurate the diagnosis. Statistical methods including inferential analysis, discriminating analysis and probabilistic methods should facilitate this process. While multivariate analyses, including linear and logistic regression, are commonly used for this purpose, factor selection and modeling is the back bone of risk score development. Inappropriate modeling substantially damages the risk score performance [85]. Moreover, while the developed risk score can be ideally used in a similar population, it should not be extrapolated to other populations or even in the same population after a few years due to life style and risk factors changes, available medications or advanced diagnostic methods for the given outcome. Therefore, they must be repeatedly validated in the target population and re-evaluated to remain applicable in clinical practice. This process would yield an equation that would predict the outcome [86]. Although linear models are relatively simple and powerful methods for prediction, their essential assumptions including normality, independence and uniformity of variance must be fulfilled to be applicable [87]. Therefore, non-linear transformation is occasionally required and regression techniques can then be used to find the best discriminant function or decision boundary. However in most clinical situations many factors have equivocal discriminatory power and risk factors have interactions and clusters overlap. As a result the data space is multidimensional [86]. In these cases, intelligent systems including artificial neural networks can improve modeling and prediction. They provide a framework by selecting the most important discriminant items and appropriate form of boundaries [86, 88, 89]. Many [85] but not all [90, 91] studies have reported that neural networks outperform conventional statistical methods. There are a few experiments of ANN application in clinical practice, including our innovative system for chronic kidney insufficiency that is already mentioned in this chapter.

4. Clustering CV risk factors: A critical appraisal

In medical science, a "*syndrome*" is defined as an "aggregate of symptoms and signs or several conditions associated with any morbid process and constituted together they produce the picture of the disease"[92]. These components are usually caused by a unifying underlying pathology and their combination confers a risk that is different from the sum of the parts. The main purpose of such a description is to help in the diagnosis, treatment and prognosis of the disease.

The Metabolic Syndrome has been a useful construct in clinical practice as well as a valuable model to understand the interactions of diverse CV risk factors. However the concept has been critically appraised for its limited validity and clinical usefulness. This necessitates a novel model for a better and more effective risk assessment in clinical practice.

The metabolic syndrome was first described by G.M. Reaven in 1988 to describe a cluster of risk factors contributing to the incidence of diabetes mellitus (DM), cardiovascular (CV) events and also mortality[93]. The definition of this syndrome remains a matter of debate and has been revised on several occasions by different organisations[94-99]. Despite some diversity, obesity, hyperglycemia, dyslipidemia and hypertension have been constant syndrome components and the central concept of such descriptions is the unity of the background pathophysiologic process and the interaction between the elements. Several epidemiologic studies have illustrated the relationship between the metabolic syndrome, CV events and mortality[100-107]; however the syndrome was recently criticised by the American Diabetes Association for its modest consistency and limited clinical application[102] and the use of the term metabolic syndrome was discouraged. Furthermore, its clinical use has recently been described as artificial, confusing and ambiguous recast of traditional risk factors [108-111], with no advantage [110] and even more false positive rate in predicting diabetes and CV disease [112] compared to the usual Framingham risk assessment. In contrast, INTERHEART, a large worldwide prospective study demonstrated that the impact of risk factor clustering is much more than simply multiplying the risk of individual factors for acute myocardial infarction[113]. Although the general clinical strategy against the presence of each risk factor (either single or in combination with others) remains constant, the threshold of interventions may differ by accepting or denying the metabolic syndrome[114]. Hence, while the current definitions are controversial, evidence-based syndrome improvement must target better clinical applicability and higher predictive power of the modifiable outcomes.

Insulin resistance is presumed to be the common pathway for all features of the metabolic syndrome[115]; yet insulin related measurements are not standardized and vary widely [116, 117]. Furthermore, despite the widespread assumption among clinicians, hyperinsulinemia and insulin resistance are not equivalent terms[102]. Besides, while 78% of individuals with metabolic syndrome have insulin resistance, only 48% of patients with insulin resistance manifest the metabolic syndrome[118]. Consequently, Leptin resistance has been suggested as an alternative mechanism which also leads to hyperinsulinemia and other metabolic syndrome features [119]. Therefore the association of hyperinsulinemia and other elements of this syndrome are not constant and many other factors may also play important roles as underlying mechanisms in clustering the risk factors. In other words, the metabolic syndrome is beyond insulin resistance, the phenomena which may simply be one of many abnormalities linked to a more fundamental, truly unifying pathophysiology [102,

120]. Likewise, the metabolic syndrome diagnosis is not always associated with a higher CV risk, for example an increased risk was not observed in elderly diabetic and non-diabetic American Indians as well as women with suspected CV disease but normal angiography[121-123]. In addition the application of different syndrome definitions can cause a 15-20% disagreement in patient classification [102] thereby changing the predictive value of the syndrome diagnosis for CV disease and mortality [101, 106, 124]. This accumulating evidence demonstrates that the association of the current syndrome components with CV disease and with each other is uncertain. Even reports supporting the metabolic syndrome state that “detecting the metabolic syndrome is only one part of the overall CV risk assessment and is not an adequate tool to estimate the 10-year risk for coronary heart disease”[125]. This is probably due to the many other related factors not included as syndrome criteria. In fact, residual analysis of many longitudinal studies demonstrates a high unexplained variance (as much as 47%) when metabolic syndrome components were considered as independent variables[102]. By and large, the current body of evidence strongly suggests that the metabolic syndrome definition needs to be standardized and additional factors included[114]. For example, despite several epidemiologic studies demonstrating the relationship between the metabolic syndrome and microalbuminuria, this factor was only incorporated into the World Health Organisation syndrome criteria in 1998 [126] which was not expressed in any other descriptions. Likewise renal failure, now accepted as an independent CV risk factor, as well as anaemia, have not been considered as a part of the metabolic syndrome. Moreover, the impact of endothelial pathology has been overlooked and cardiac disease has been considered simply as an outcome and not an interacting part of the syndrome.

We have introduced the term of “*circulatory syndrome*” as a more refined clinical construct which is composed of many disease markers including **Metabolic, Arterial, Renal** and cardiac components (simply abbreviated as: “**MARC**”)

5. Circulatory (MARC) syndrome

Circulatory syndrome is a cluster of *risk markers* with synergic effects. The proposed syndrome consists of eight major components (Figure 5), as follows (in the “MARC” order):

- Abnormal glucose metabolism
- Dyslipidemia
- Hypertension
- Arterial stiffness
- Microalbuminuria
- Renal impairment
- Anaemia
- Left ventricular dysfunction

All of these “markers” occur on a background of oxidative stress, inflammation, hypercoagulability and endotheliopathy (*underlying factors*) and can be accelerated by factors such as aging, obesity, smoking and physical inactivity (*predisposing factors*). Furthermore they can be simply and non-invasively assessed in outpatient clinical settings. While the mechanisms underlying the circulatory syndrome are poorly understood, it must be strongly stated that *vascular-endothelial pathways* link all and are of pathological

significance. Activation of the renin-angiotensin system, insulin resistance and increased sympathetic activation are all by-products of the underlying pathogenic process. Since these markers represent the extent of the underlying disease process, they could also manifest as risk factors for other components and thereby enhance their development. Considering the interrelationships, the final outcome in this model can be considered to be CV events, stroke or renal failure; all of which are associated with general circulatory health. Consequently the condition of the circulatory system and these markers is directly related to the mortality rate.

Primordial studies demonstrate a robust and valid utility of the "MARC" syndrome concept and a useful risk assessment approach in chronic kidney disease and diabetes mellitus. However, larger prospective cohorts are required for further validation of the concept.

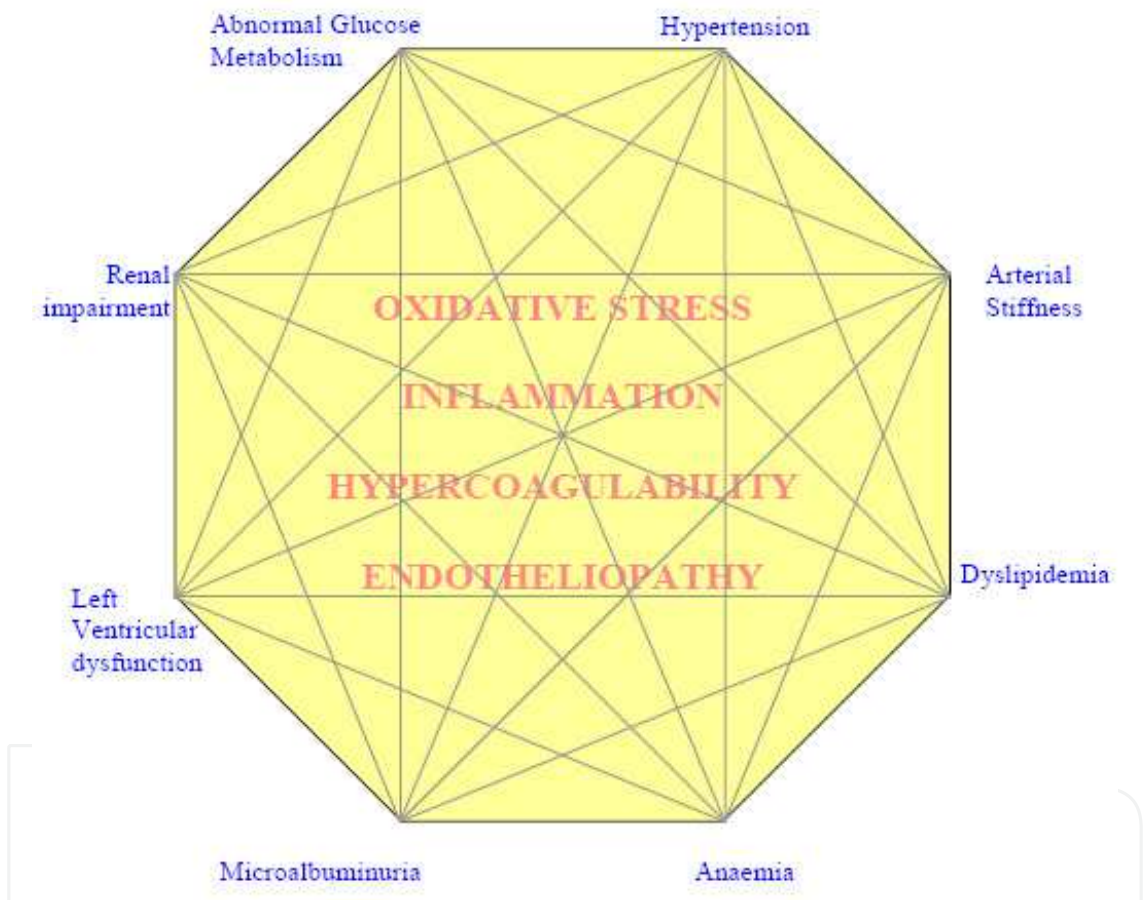


Fig. 5. An illustrative **Circulatory Syndrome**; A cluster of cardiac, renal, arterial and circulatory markers of disease that are interconnected through the endothelium; the common media (**underlying factors**) include oxidative stress, inflammation, hypercoagulability state and endotheliopathy which contribute in the main mechanisms of the phenomena; the third dimension (**precipitating factors**) include age, obesity, physical inactivity and smoking which accelerate the phenomena.

Rationale For Inclusion Of The Components

The Circulatory Syndrome shares some elements with the metabolic syndrome. However it includes additional metabolic and non-metabolic factors (Table2).

Abnormal Glucose Metabolism Fasting Plasma Glucose >6.1 mmol/l ; or 2hr post prandial >7.8 mmol/l
Hypertension SBP≥130 mmHg; and/or DBP≥ 85 mmHg
GFR MDRD eGFR <90 ml/min/1.73 m ²
Microalbuminuria Urinary Albumin creatinine ratio (ACR) [two occasions] >2.5 (male) >3.5 (female)
Arterial Stiffness Upper quartile for PWV, AI or ambulatory PP in the population
Left ventricular dysfunction Any evidence of systolic or diastolic; Imaging techniques or Exercise test (MET <6, impaired systolic BP response) or BNP> 100 pg/ml Previous myocardial infarction
Anemia Hb< 12 female HB<13 male
Dyslipidemia Triglyceride ≥ 1.7 mmol/l or HDL<1 (male) or <1.3 (female) mmol/l or Elevated Apolipoprotein B

GFR: Glomerular Filtration Rate, PWV: Pulse Wave Velocity, AI: Augmentation Index, PP: Pulse Pressure, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MET: Estimated multiples of resting oxygen uptake, BNP: Brain Natriuretic Peptide, HDL: High Density Lipoprotein

Table 2. Preliminary Diagnostic Criteria for Circulatory Syndrome;

(1) Abnormal glucose metabolism: Diabetes and abnormalities in glucose metabolism are well known risk factors for cardiac, arterial and renal disease as well as anemia [127, 128]. Although insulin resistance and hyperinsulinemia can be attributed to these complications, they may occur with or without insulin resistance because several other mechanisms including advanced glycation end products, autonomic nervous instability, imbalance between the renin-angiotensin system and nitric oxide, hemodynamic changes and endothelial dysfunction with subsequent ADMA accumulation (an inhibitor for nitric oxide synthesis) and adiponectin deficiency also contribute in the process [120, 129, 130]. Furthermore, albuminuria, arterial stiffness and intima media thickness increase with the increasing number of metabolic syndrome components even before fulfilling the diagnostic criteria for the syndrome, particularly amongst subjects with type 2 DM [131]. In addition,

alterations in BP circadian rhythm and BP profile including non-dipper nocturnal BP is now considered as a manifestation of arterial remodelling and is associated with other manifestation of endothelial dysfunction including mA and arterial stiffness.

(2) Lipid abnormalities: Dyslipidemia including increased LDL and TG as well as low HDL is a major risk in patients with chronic renal disease, hypertension and diabetes [105, 132-134]. Genetic variants of lipoprotein lipase correlate with the presence and degree of albuminuria [135]. Dyslipidemia is an independent determinant of progression toward chronic kidney disease and is a known cardiac risk factor [28, 44]. It also contributes to arterial micro-inflammation and atherosclerosis [136]. From different perspective, the correction of lipid abnormalities can reduce albuminuria in subjects with the metabolic syndrome [137], decrease inflammatory markers [138], improve renal function [139], increase arterial compliance [140], improve left ventricular function [138] and prevent CV events [136]. It is noteworthy that obesity was not incorporated into our criteria since there is an opposite relationship between BMI and survival in CKD (reverse epidemiology) [108] and therefore less obese patients with CKD reach to ESRD.

(3) Blood pressure abnormalities: Hypertension is introduced as the leading risk factor of death according to WHO report of global health [4]. Hypertension and altered blood pressure circadian rhythm are common co-morbidities with diabetes and pre-diabetic states as well as kidney disease [141]. BP is strongly associated with arterial stiffness and promotes left ventricular dysfunction [29]. In the setting of insulin resistance the vasodilatory effect of insulin can be lost but its renal sodium reabsorption stimulation is preserved. In addition, insulin-induced sympathetic activity increases the prevalence of hypertension in the metabolic syndrome [120]. Furthermore, while salt sensitivity is associated with impaired glucose metabolism, oxidative stress, dyslipidemia and insulin resistance [142, 143], it also increases efferent glomerular arteriolar tone and thereby raises glomerular capillary pressure and proteinuria [144] as well as inducing blood pressure abnormalities via renal sodium reabsorption and sympathetic overactivity [145].

(4) Arterial stiffness: Decreased arterial compliance is influenced by both atherosclerosis and arteriosclerosis, as well as functional arterial abnormalities [29, 146]. It occurs very early in the process of kidney disease and DM [147, 148], even preceding microalbuminuria [149] and has also been observed in normal individuals with a close family history of DM [148]. Recent studies have illustrated that increased central arterial stiffness in hypercholesterolemia, even in newly diagnosed individuals, is associated with low-grade systemic inflammation [150, 151]. Arterial stiffness in turn increases LV load and leads to ventricular stiffness and diastolic dysfunction [152, 153]. It has also been suggested as the linking factor between renal impairment and CV diseases [25]. Of great importance, decreased arterial compliance predicts mortality in variant patient groups, independently from other risk factors [38, 154-156].

(5) Microalbuminuria is now accepted as a marker of renal, cardiac and arterial damage being predictive for the further development of CV events, renal failure and DM [25, 134]. It is also closely associated with the prevalence of anaemia [128], hypertension [157] and metabolic syndrome components [131]. Microalbuminuria commonly occurs early in subjects with abnormal glucose metabolism [147, 158] and is correlated with dyslipidemia [159], arterial stiffness [160, 161] and increased coagulability [162] as well as inflammatory

markers[163, 164]. Furthermore the presence of microalbuminuria predicts ventricular dysfunction, coronary heart disease and exercise intolerance[165, 166].

(6) Renal impairment: Kidney function can not be isolated from the health of the heart and arteries and is also associated with the metabolic syndrome components. Alterations in glomerular structure are seen very early in the obesity-mediated metabolic syndrome[82]. Renal hemodynamic reserve is already impaired in patients with asymptomatic left ventricular dysfunction [167]. In addition, the kidney has an important role in insulin and glucose metabolism [168] and insulin resistance has a predictive value for chronic kidney disease [82, 95]. Renal function has been called the Cinderella shoe of CV risk profile [169] and the impact of even minor renal dysfunction on CV function is now well established [25] with endothelial cell dysfunction is likely to be the linking factor between renal and cardiac disease[25, 134, 170]. However endothelial dysfunction in turn is a consequence of inflammation and oxidative stress and is accelerated by these phenomena[171] and is also correlated with a number of the metabolic syndrome components [131]. Decreased arterial compliance increases ventricular wall tension and stiffness and consequently diastolic dysfunction[153]. This in turn may lead to partial renal ischemia, followed by activation of the renin-angiotensin system and tubulointerstitial damage[170]. On the other hand, hyperfiltration which is observed in the early stages of diabetic nephropathy and hypertension [172, 173], leads to increased glomerular pressure and resultant sclerosis which in turn accelerates hypertension[141].

(7) Anemia: Anemia is a common finding in DM and has multifactorial mechanisms[128]. Early tubulointerstitial occurs which disease decreases EPO production and moreover inflammatory cytokines reduce EPO responsiveness leading to anaemia[174]. It is also associated with the level of albuminuria[128]. Anaemia in turn, increases the progression toward CKD, oxidative stress, tissue ischemia, ventricular stress and mortality[175-177]. Of interest, a recent study demonstrated the contribution of anemia to the frequent diastolic dysfunction in DM, as well as its association with brain natriuretic peptide (BNP) and suggested using this factor to identify diabetic patients at increased risk of cardiac dysfunction [175]. Therefore, accumulating evidence has introduced anemia as an important risk factor for the circulatory system. On the other hand, correction of anemia improves the prognosis in chronic kidney disease, heart failure and DM and its complications as well as decreasing mortality [177-179]

(8) Left Ventricular dysfunction: In contrast to the metabolic syndrome, ventricular function is proposed as an interactive part of the circulatory syndrome. This idea is supported by reports of a lack of a relationship between the metabolic syndrome and mortality in individuals who have good cardiorespiratory fitness [180]. On the other hand even a mild stage of ventricular failure, as manifested by impaired exercise response is predictive for mortality[181, 182]. Ventricular function determines blood pressure and renal perfusion and in turn is influenced by kidney function, anemia and arterial stiffness and microalbuminuria [153, 183]. Diastolic dysfunction occurs early in DM, is correlated with arterial stiffness and affects exercise response [184]. Furthermore, it has been reported that asymptomatic patients with type 2 DM have subclinical ventricular dysfunction which is related to glycated hemoglobin and LDL cholesterol [185]. Also a recent in vitro study demonstrated that myocyte relaxation and Ca^{2+} handling are abnormal in early uremia, leading to uremic cardiomyopathy [186].

Additional evidence: It is of great interest that some hypoglycaemic agents reduce blood pressure via suppression of the renin-angiotensin system and some ACE inhibitors can reduce insulin resistance in addition to reducing microalbuminuria and arterial stiffness, which raises the possibility of the presence of a common pathway for the adverse effects of hyperglycemia and hypertension[187-189]. Likewise, some lipid lowering agents may exhibit mild anticoagulant and hypotensive effects [190] and angiotensin inhibitors have anti-inflammatory actions [191] which also indicate a possible common source of these abnormalities.

It could be expected that genetic predisposition including nephron underdosing, ACE gene polymorphism, congenital tubular defects and also some other factors such as aging, obesity and smoking produce organ damage susceptibility [133, 192-194].

The above evidence suggests that a genetic profile or a common pathologic process induces a network of metabolic (including alterations in glucose, salt, insulin and lipid metabolism) and hemodynamic abnormalities (due to renin-angiotensin system stimulation, sympathetic overactivity and decreased nitric oxide bioavailability) which are followed by anaemia, hypercoagulability, tissue ischemia, arterial stiffness, hypertension, renal and cardiac dysfunction, the other features of the circulatory syndrome (figure 5).

Underlying Pathology

It is proposed that inflammation is the fuel that “burns” the circulatory syndrome. The association between inflammatory markers and both DM and hypertension is so strong that these diseases has recently been redefined as inflammatory diseases, as has atheroma[195-198]. Advanced glycation end products (AGEs) which accumulate in DM activate inflammatory cells[195]. Likewise, insulin resistance has a strong link with inflammation, although additional mechanisms including genetic factors may influence this relationship[199]. In addition, high LDL cholesterol induces oxidative stress and increases inflammation[200]. On the other hand HDL and apolipoprotein A1 have anti-inflammatory and anti-oxidant properties[201]. Hence, metabolic elements of the syndrome are correlated with inflammation.

Inflammation is known to be a modifier of the relationship between microalbuminuria and hypertension [163, 202]. Hence, CRP has been frequently promoted as a part of the metabolic syndrome [102, 125, 203]. Moreover, inflammatory markers such as CRP are now considered to be independent predictors of DM [195] and its complications including left ventricular hypertrophy, endothelial dysfunction, albuminuria and renal failure [25, 171, 204, 205].

There is a close relationship between inflammation and hypercoagulability [164, 206]. Furthermore, hypercoagulability is also linked to the metabolic syndrome, dyslipidemia, anaemia and even the hemodynamic response to exercise [201, 207-209]. It is also associated with a poorer outcome in coronary artery disease, heart failure and is correlated with the severity of target-organ damage including renal impairment [210-212]. Consequently, diabetic and metabolic syndrome patients are at high risk for thrombotic events [213-215] and have an increased level of clotting factors including tissue plasminogen activator (tPA) and von Willenbrand Factor (vWF) and D-dimer when compared to the controls[216]. Additionally, insulin and lipids may have direct inhibitory effects on coagulation and platelet function through nitric oxide, a pathway that is impaired in DM patients [217].

By and large, this interlinking mesh of inflammatory mediators, oxidative stress, endotheliopathy and hypercoagulability makes a common soil for development of the circulatory (MARC) syndrome.

6. New targets and novel approach to CVD risk modification

The above description of the “circulatory syndrome” clearly has clinical applications. The identification of commonly evaluated markers such as blood pressure, glucose and lipids in a patient should also prompt a search for other markers which make up the circulatory syndrome. A suspected circulatory syndrome should facilitate decision making for diagnostic procedures in asymptomatic but high risk patients. Also treatment of each syndrome component should be accompanied by management of the other components. Furthermore, any difficulty in treating one circulatory syndrome marker should probably leads to a more aggressive treatment program for other components as is currently proposed in patients with renal disease, diabetes and associated hypertension. Hence, management of the proposed "Circulatory Syndrome" would need an interdisciplinary approach with the collaboration of different medical subspecialties.

7. A novel approach to diabetic nephropathy (DN)

The evidence of the close relationship of DM, hypertension, renal function, cardiac function, arterial compliance and metabolic factors have already been discussed. Accordingly the proposed concept of the “*Circulatory Syndrome*” could be applied as a novel approach to DN. This approach should overcome the potential barriers to achieving target points in DM and enhance medications efficacy. According to this new perspective, the treatment of co-morbidities in DM including heart failure, renal failure, arterial stiffness, anemia and the hypercoagulability state as well as reducing any potential inflammation source (e.g. chronic infections, immunology-mediated disease and sensitivities) should enhance adherence to the target points and disease control. This needs a “*multidisciplinary approach*” to CV risk management in DM, in which a clinical epidemiologist or a care plan manager must have a central role. Additionally a global risk score is preferred to the current target points for each risk factor so that the threshold of intervention is clearly defined based on several potential risk factors and assessment of adherence to the guideline is estimated by risk score alterations.

8. New markers

Given the serious limitations of using mA as a single disease marker in screening [31], a multifactorial approach is required to boost screening efficacy and allow reliable risk estimation in DN. The Japanese Society of Nephrology is the only professional organization that has formally added renal hypertrophy and urinary type IV collagen to their guideline as early markers of the existence of DN [218]. There is also evidence for other potential markers including glomerular, tubular, interstitial, endothelioarterial, genetic and cellular markers. However their applicability, validity and reliability must be investigated in a parallel test with mA.

These markers help risk stratification for patients without mA or with fluctuating proteinuria. Furthermore, they facilitate diagnosis of other facets of diabetic kidney damage and also explain the link between cardiac and renal complications of DM.

9. New strategies

The threshold of action for screening, intervention and assessment must be revised based on current DN knowledge and should be followed by altered strategies to define high risk patients. It should also include all pathological aspects of DN including those proposed in the “Circulatory Syndrome”, although these will need to be refined, particularly in asymptomatic patients.

In terms of treatment, research findings about renal benefits of the renin-angiotensin-aldosterone system (RAAS) blocking irrespective of blood pressure and albuminuria [219] have not fully integrated into Clinical practice guidelines. Likewise, while recent research has demonstrated advantages of lipid lowering agents even in patients with normal lipid levels [220], the threshold for action remains at higher levels. Similarly, treating anemia has a significant impact on renal function preservation even in early stages of renal disease and erythropoietin therapy has potential advantages for cardiac, neural, endothelial and renal protection [221] as well as a general benefits due to reduction in the oxidative stress, insulin resistance and cytokine accumulation in DM patients (as mentioned in our recently published paper [222]); yet decision criteria are not completely clear in this regard. With accumulating evidence, the threshold for anemia correction is expected to be reduced in a near future.

Regarding follow-up, recent reliable and practical assessments should be considered including central and/or ambulatory BP. Also for renal function, eGFR (based on the MDRD or the Cockcroft-Gault formula) is superior to plasma creatinine [223].

10. New treatment targets

It might be argued that with considering the circulatory syndrome concept and increasing number of the action sites, the number of medication is ought to be increased. Then since increased number of medications usually leads to reduced patients’ compliance, such an approach may not only fail to improve disease control, but also make the problem more complex. While possibly true, there are potential solutions. For instance many experts encourage “poly-pills” which include a combination of the required agents. Although it may have better patients’ acceptance, it cannot reduce the potential adverse effect of polypharmacy. Alternatively and ideally, the type of treatment must be revised in order to meet multiple targets using a single medication (“super-pills”).

New treatment options: The marked advantages of using ACE-I and ARB has been appreciated with a 60-70% risk reduction the risk of progression to overt nephropathy in several large clinical trials [224-226]. However this optimistic result would not be completely achieved in routine practice and they can not abrogate the progression of kidney disease. This may suggest incomplete blockage of the RAAS by current medication dose which allow “aldosterone synthesis escape” [227]. Although a recent meta-analysis of randomized trials with ACE-Is and ARBs yielded only a small renoprotection benefit (and no benefit in DM) and demonstrated a smaller benefit in large studies [228], it contradicts previous meta-analysis [229, 230] and seems to be biased by the accessory results from the Antihypertensive and Lipid Lowering treatment to prevent Heart attack Trial (ALLHAT) which was not originally designed for renal outcome evaluation [231].

A combination with beta blockers or calcium channel blockers or a diuretic was previously recommended in the practice guidelines, newer combinations of ACE-I and indapamide, ACE-I and spirinolactone and a double blockage of RAAS (ACE-I and ARB) have been demonstrated promising in terms of lowering BP and mA, which is also supported by the new understanding of ACE-2 enzyme, angiotensin receptor-2 and the role of aldosterone in CKD progression [232]. In addition, using pioglitazone or rosiglitazone in combination with sulphonylurea with or without metformine has also been suggested by experts as an effective combination; however the available clinical data is still limited. Finally, it is noteworthy that while identification and management of hypertensive patients with elevated heart rate (with beta-blockers or calcium antagonists) is recommended by expert consensus [233], non-selective beta blockers (e.g. propranolol) generally decrease GFR by lowering cardiac output. In contrast, the β_1 -selective agents (e.g. metoprolol and atenolol) may have a beneficial effect on declining GFR as well as protecting heart against heart failure. However these may also have adverse effect on plasma glucose and atenolol must be adjusted in renal failure due to its impaired renal clearance. On the other hand non-selective vasodilating beta blockers (Carvedilol and Labetalol) not only reduce BP but also have antioxidant and renoprotective effects [234]. Finally, considering of erythropoietine (EPO) in medical management of diabetes is expected to improve CV health in DM [222, 235].

New agents: Several animal models have suggested many potential candidates for prevention and treatment of DN. Renoprotective effect of ALT-711 (a cross link breaker of the advanced glycosylation end product), ruboxistaurin (an inhibitor for protein kinase C), eplerenone (a new aldosterone antagonist), thiamine and a modified heparin glycosaminoglycan have been reported, as being effective in reducing albuminuria and renal lesions [232, 236, 237]. However, very few human studies have been conducted in human of which the combination of ACE-I and omapatrilat (an endopeptidase inhibitor), sulodexide (a glycosaminoglycan), Pirfenidone (TGF- β inhibitor) and pimagedine (a second generation inhibitor of advanced glycation end product) have had dramatic beneficial effects in DM patients [232, 236, 238]. There are also some evidence of the efficacy of folic acid on endothelial function improvement in different groups of patients including type 2 DM [239].

Developing novel drugs opposing the action of TGF- β , connective tissue growth factors, cytokines and reactive oxygen species is the next step. Also by recognizing the role of relaxin [240], urotensin II [241] and vascular calcification contributors, additional medication might one day be available.

Multipotential agents: Accumulating evidence demonstrates the multidimensional action of some medications on glycaemic and BP control, reducing lipid and mA and improvement in arterial compliance. For instance, blocking of the renin-angiotensin system has anti-diabetic and anti-inflammatory effects as well as antihypertensive actions and improves mA and arterial stiffness at the same time [187, 189, 191]. This also applies to some lipid lowering agents [190, 220]. Likewise, insulin-sensitizing thiazolidinediones (TZDs) ameliorate mA and are antihypertensive [242]. Also metformin improves both endothelial function and the metabolic syndrome [243]. From a different point of view, treating anemia with erythropoietin may also have cardiac, renal, neurohormonal and metabolic benefits due to anemia correction of anemia and the cytoprotective effects of erythropoietin *per se* [221, 222, 244]. Several researches are being conducted to introduce and develop novel EPO replacement therapies such as synthetic erythropoietic proteins, continuous EPO receptor

activators (CERA), EPO gene transfer using retroviral vectors and implementation of EPO producing cells in A-V fistula graft which will create a revolution in related therapies [222].

With the axial role of RAAS in the pathogenesis of DN, non-hemodynamic effects of ACE-I and ARB including their action on TGF- β , extracellular matrix and cytokines have the focus of several studies in recent years [237]. According to a recent study Losartan improves resistance artery lesions and prevents TGF- β production in untreated hypertensive patients [245]. In addition, ACE-I agents potentiate bradykinin-induced tissue plasminogen activator (t-PA) release leading to endothelial fibrinolytic function [246, 247]. Consequently several studies have indicated that the renoprotective of these drugs is independent of their antihypertensive effect [229].

The recognition of a new class of nuclear receptors named "peroxisome proliferators-activated receptor" (PPAR) has provided an additional field for action against DN and consequently its CV complications. Rosiglitazone is a PPAR- γ agonist which was demonstrated as being effective in lowering blood pressure and reversing insulin resistance [248]. Likewise, several studies have verified the multipotential action of PPAR- α agonists including Fenofibrate in reducing fasting blood glucose, ameliorating insulin resistance, decreasing mA, correction of lipid metabolism, suppressing collagen by mesangial cells, preventing glomerulosclerosis as well as antihypertensive [242, 249]. This body of evidence supports the potential impact of multipotential drugs in the future treatment of DN.

11. Conclusion

Early diagnosis and management of CV risk, particularly in diabetes and chronic kidney disease requires a new insight and subsequently a novel approach to the disease is mandatory. While our studies demonstrated various facets of the interactions between renal, cardiac, arterial and metabolic factors, the proposed "*Circulatory Syndrome*" can facilitate formulation of new strategies for the better diagnosis and management of CV risk. Accordingly, a multidisciplinary evaluation of glycemic control, lipids, anemia, blood pressure profile, albuminuria, GFR and ventricular function as well as an assessment of arterial compliance (as an axial element) provides adequate information for early and effective identification of high risk patients for progression toward CVD. The proposed concept of the "*Circulatory (MARC) Syndrome*" is expected to facilitate this revolution by a multidisciplinary approach.

12. References

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Cardiovascular risk factors contribute to the development of cardiovascular disease from early life. It is thus crucial to implement preventive strategies addressing the burden of cardiovascular disease as early as possible. A multidisciplinary approach to the risk estimation and prevention of vascular events should be adopted at each level of health care, starting from the setting of perinatology. Recent decades have been marked with major advances in this field, with the emergence of a variety of new inflammatory and immune-mediated markers of heightened cardiovascular risk in particular. The current book reflects some of the emerging concepts in cardiovascular pathophysiology and the shifting paradigm of cardiovascular risk estimation. It comprehensively covers primary and secondary preventive measures targeted at different age and gender groups. Attention is paid to inflammatory and metabolic markers of vascular damage and to the assessment of vascular function by noninvasive standardized ultrasound techniques. This is a must-read book for all health professionals and researchers tackling the issue of cardiovascular burden at individual and community level. It can also serve as a didactic source for postgraduate medical students.

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