Multifactorial intervention in metabolic syndrome targeting at prevention of chronic kidney disease—ready for prime time?

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The term metabolic syndrome (MetSyn) indicates a constellation of risk factors associated with increased burden of atherosclerotic disease [1]. Despite some controversy regarding its existence as a distinct entity [2], accumulating evidence suggests that individuals with MetSyn are at increased risk of cardiovascular events and type 2 diabetes [3,4]. Several factors such as obesity, insulin resistance, physical inactivity and advancing age seem to constitute its pathophysiological basis [1,5]. The prevalence of MetSyn depends on the studied population and the definition used but in Western populations more than 20% of adults are affected [6]. Current ‘popular’ definitions of MetSyn, such as that of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III, the National Heart, Lung, and Blood Institute and the American Heart Association (NHLBI/AHA) and especially that proposed by the International Diabetes Federation (IDF) (Table 1) are continuously evaluated as to whether they can identify high-risk population for cardiovascular disease and diabetes who would benefit from intensive behavioural and/or pharmacological treatment [7,8].

Metabolic syndrome and chronic kidney disease

In addition to the aforementioned relationships, there is substantial evidence of an association between MetSyn, obesity and both albuminuria and chronic kidney disease (CKD) [9–17]. In the cross-sectional NHANES III study [9], participants with MetSyn had an odds ratio (OR) of 2.60 of having CKD compared to those without the syndrome, while in the prospective cohort ARIC study [12] MetSyn was associated with an increased risk of incident CKD (OR: 1.43). Notably, a clear positive relationship between the number of MetSyn components and CKD risk was apparent in both studies [9,12]. Similar observations have been recently reported in Asian populations [13,14]. Furthermore, MetSyn has been clearly associated with microalbuminuria, a marker of endothelial damage that per se represents an independent cardiovascular risk factor [9,15].

Besides the well-known role of diabetes and hypertension in the development and progression of CKD, obesity has emerged as a risk factor for deterioration of renal function. Obesity is the hallmark of MetSyn and is characterized by insulin resistance, hyperinsulinaemia and dyslipidaemia [10]. It should also be borne in mind that insulin resistance and hyperinsulinaemia have deleterious effects on the kidney, increasing the CKD risk [10,11,18]. In fact, central obesity, as assessed by the waist circumference, has been indicated as an independent risk factor for renal dysfunction [9,12,14,16,19]. It has also been demonstrated that increased body mass increases the risk for developing end-stage renal disease (ESRD), even after adjustment for hypertension, proteinuria and other commonly associated conditions [20,21]. The main pathophysiological mechanisms (regardless of the presence of hypertension or diabetes) include increased glomerular filtration rate (GFR) and altered renal haemodynamics, inflammatory and oxidative changes, excess renal sodium reabsorption and activation of the renin–angiotensin and sympathetic nervous systems [16]. These abnormalities possibly cause the so-called ‘obesity-related glomerulopathy’ consisting of glomerulomegaly and focal segmental glomerulosclerosis [16,19].

The renin–angiotensin–aldosterone system (RAAS) is currently considered an important pathophysiological factor in the development of MetSyn, which can also contribute to the high cardiovascular risk of patients with this syndrome. Recent studies have
suggested that aldosterone, the last step in the RAA cascade, is associated with features of MetSyn. Two large studies have reported that plasma aldosterone, but not plasma renin levels, are associated with MetSyn [22,23] and markers of insulin resistance [23] in normotensive and hypertensive blacks. However, no evidence for elevated aldosterone or plasma renin activity was found in individuals with high-normal blood pressure and the MetSyn in a recent TRial Of Preventing HYpertension (TROPHY) sub-study [24] In this study, 82% of patients were white, raising the issue of a race-specific effect. Recent data from Colussi et al. [25] extend the evidence of a significant association between aldosterone, hyperinsulinaemia and insulin resistance to white subjects. The underlying mechanism by which aldosterone is potentially linked to MetSyn has been investigated in experimental work, showing that an oxidized derivative of linoleic acid, a fatty acid that is increased in obesity, can stimulate aldosterone secretion by rat adrenal cells and correlates positively with plasma aldosterone and blood pressure in humans [26]. It has been speculated that angiotensin II can lead to insulin-resistance by inducing oxidative stress and to the development of salt-sensitive hypertension by promoting sodium reabsorption in the proximal tubules, thereby explaining the favourable impact of blockers of the RAS on the prevention of new cases of diabetes [27].

The association of CKD with other MetSyn components is less well studied. Epidemiological data indicate that hypertriglyceridaemia and low levels of high-density lipoprotein (HDL) cholesterol are independent risk factors for the development and progression of CKD, although the underlying mechanisms have not been examined [9,12,28,29].

### CKD and cardiovascular disease

A growing body of evidence indicates that CKD adversely affects cardiovascular morbidity and mortality [30,31]. It has been demonstrated that in patients with GFR <60 ml/min/1.73 m² there is an inverse relationship between the degree of GFR reduction and cardiovascular risk, independent of known risk factors, history of cardiovascular disease and presence of proteinuria [30]. Furthermore, it has been recently suggested that subtle or minor renal function decays (GFR 60–90 ml/min/1.73 m²), even in apparently healthy individuals, have a negative impact on cardiovascular morbidity and mortality [31,32]. The principal factors that have been implicated in the pathophysiology of increased cardiovascular risk in CKD include pressure/volume overload and anaemia that lead to left ventricular hypertrophy, alterations in calcium metabolism that result in valvular and vascular calcifications, inflammation, oxidative stress, endothelial dysfunction and sympathetic hyperactivity [33]. Undoubtedly, CKD per se represents on its own a metabolic syndrome with malnutrition that further feeds the cardiovascular risk and the deterioration of renal function, leading to a vicious cycle [34].

### Importance of CKD prevention in MetSyn

Current epidemiological evidence suggests that obesity and MetSyn represent a growing epidemic with a significant impact on the health status [35,36]. In light of these findings, it is reasonable to assume that the number of patients who are at risk for developing CKD is continuously increasing. Taking into consideration the well-established associations of CKD with

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**Table 1. Diagnostic criteria of the metabolic syndrome according to different definitions**

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<td>Central obesity</td>
<td>&gt;102 cm</td>
<td>&gt;102 cm</td>
<td>&gt;94 cm</td>
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<td>&gt;88 cm</td>
<td>&gt;88 cm</td>
<td>&gt;80 cm</td>
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<td>Hypertension</td>
<td>BP ≥135/85 mmHg</td>
<td>BP ≥135/85 mmHg</td>
<td>BP ≥135/85 mmHg</td>
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<td>or specific medication</td>
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<td>Triglycerides</td>
<td>≥150 mg/dl (1.7 mmol/l)</td>
<td>≥150 mg/dl (1.7 mmol/l)</td>
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<td>or specific medication</td>
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<tr>
<td>HDL-cholesterol</td>
<td>&lt;40 mg/dl (1.03 mmol/l)</td>
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<tr>
<td>Fasting plasma glucose</td>
<td>≥110 mg/dl (6.1 mmol/l)</td>
<td>≥100 mg/dl (5.6 mmol/l)</td>
<td>≥100 mg/dl (5.6 mmol/l)</td>
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*For subjects of European origin.*
ESRD and cardiovascular morbidity and mortality, the importance of timely and effective prevention of renal dysfunction in the setting of MetSyn is apparent.

**Multifactorial intervention in MetSyn and CKD prevention**

The concept of intensive multifactorial intervention is based on the fact that MetSyn represents a clustering of risk factors and therefore each of its components should be treated aggressively in order to obtain an optimal clinical benefit (Figure 1). In this context, the implementation of therapeutic strategies targeting at common pathophysiological pathways may simultaneously affect several components of the syndrome. The value of this multifactorial approach in preventing cardiovascular events or CKD in the setting of MetSyn has not been examined. The only study that tested such a mode of treatment was performed in patients with MetSyn and non-alcoholic fatty liver disease showing that the intensive integrated intervention significantly attenuates this hepatic complication [37]. Interestingly, the intensified multifactorial intervention has been investigated in type 2 diabetic patients [38]. In the Steno-2 trial, a multiple risk factor intervention having strict treatment targets was performed [39]. In specific, high-risk diabetic patients with microalbuminuria were managed by a stepwise approach with lifestyle and diet modifications, and pharmacologic therapy targeting at hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria [39]. It was demonstrated that the patients who received intensive therapy had a lower risk of cardiovascular disease and nephropathy compared to those in the conventional treatment group [39]. Moreover, the absolute 20% reduction in the risk of

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**Fig. 1. Management of the metabolic syndrome. CVD, cardiovascular disease; GFR, glomerular filtration rate; MetSyn, metabolic syndrome; ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor antagonists; OGTT, oral glucose tolerance test.**
cardiovascular events was higher than that in studies examining single-factor intervention strategies aimed at hyperglycaemia, hypertension or dyslipidaemia [38]. This clinical trial may be considered a possible model for treatment of the multiple risk factors in the MetSyn. Its results reinforce the notion that aggressive multi-targeted management of the MetSyn may confer protection for cardiovascular disease and CKD.

An increasing number of reports indicate that specific treatments and interventions used for the management of individual MetSyn components can protect the kidney. It could therefore be speculated that a multifactorial therapeutic approach possibly confers optimal benefits in the prevention and modulation of CKD. Inevitably, the high cardiovascular risk that accompanies both MetSyn and diabetes and CKD implies an aggressive preventive care [40].

Lifestyle modifications including dietary interventions, weight reduction and physical activity represent an integral part of the multifactorial approach. The NCEP and, particularly, the IDF (Table 1) have taken the position that obesity (especially abdominal obesity) is a dominant factor behind the multiplication of risk factors [6]. Weight reduction improves insulin sensitivity and may have a favorable effect on renal function. Chagnac et al. [41] have showed an improvement in obesity-related glomerular hyperfiltration after weight loss, in subjects without overt renal disease. Studies examining the effect of weight loss on obesity-related glomerulopathy are lacking. Interestingly, a dramatic reduction of urinary protein excretion was observed in an obese patient after rapid weight loss [42]. Moreover, it has been demonstrated that drastic weight loss after bariatric surgery results in a gradual amelioration in 24 h albuminuria, even 2 years after the operation [43]. The impact of agents used for weight reduction on renal function is not known.

Physical activity exerts beneficial effects on the metabolism of glucose and lipids, reduces inflammation, and improves endothelial dysfunction. Of note, physical inactivity has been associated with CKD, especially in men [44]. On the other hand, a recent analysis of the NHANES III study revealed a clear association between physical activity and GFR in patients without MetSyn, but GFR correlated only with activity variety (number of different activities) in subjects with MetSyn [45]. Hence, the merit of physical activity for prevention of CKD in MetSyn, as well as the type and intensity of exercise that have potential benefits, requires further study.

Several pharmacologic agents targeting individual components of MetSyn may also have favorable effects on CKD. Intensive treatment of diabetes and hypertension prevents the development of microalbuminuria and diabetic nephropathy but its exact value in the setting of MetSyn has not been clarified yet [16]. Agents that block the renin–angiotensin system have the potential to confer renal and cardiovascular protection [46,47]. RAAS blockade is strongly recommended by most recent guidelines as the initial regimen of choice for renoprotection based on the results of several clinical trials and meta-analyses. With hardly any exception, these trials have revealed larger reductions in proteinuria as well as a diminished progression to the development of renal endpoints with RAAS blockade compared with other antihypertensive regimens in both diabetic and non-diabetic nephropathies [48]. Indeed, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are the preferred antihypertensive drugs in patients with MetSyn as in the case of diabetics [5]. Bearing in mind that besides their antihypertensive activity these agents have pleiotropic effects, it is tempting to speculate that such a treatment could provide renal protection even in the absence of hypertension.

Strict glycaemic control is of paramount importance in diabetic patients. It has also been proposed that early intervention in the pre-diabetic state may retard the onset of overt diabetes and attenuate several associated abnormalities and complications. Agents that improve insulin sensitivity are of great interest but at the same time, concerns have been raised. For example, metformin reduces the development of diabetes in prediabetic individuals and decreases macrovascular events in diabetics [11,16]. Nevertheless, it is contraindicated when renal failure is present (i.e. creatinine clearance <60 ml/min according to the package insert from the manufacturer) [49]. Recent evidence suggests that the introduction of estimated GFR reporting [eGFR, calculated using the abbreviated modification of diet in renal disease (MDRD) equation] could have a major effect on prescription of metformin [50]. A threshold eGFR of 36–40 ml/min/1.73 m² is currently considered safe in clinical practice [50]. Thiazolidinediones, a novel class of antidiabetic agents that interact with the peroxisome proliferator activator receptor-γ (PPAR-γ) causing insulin sensitization, have multiple pleiotropic effects [51]. Apart from the hypoglycaemic effect, they reduce blood pressure and modulate dyslipidaemia, inflammation, oxidative stress, endothelial dysfunction, fibrosis and remodelling, glomerular cell proliferation [51,52]. Moreover, accumulating data from animal and human studies support the notion that thiazolidinediones reduce urine albumin excretion and may prevent the development of CKD [52]. However, their use causes weight gain and fluid retention, an undesirable effect, especially for obese subjects.

Statins represent the most effective and widely used agents for the management of hyperlipidaemia, while providing considerable cardiovascular protection [53]. The role of statins in MetSyn has not been well-studied. Placebo data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) and the Scandinavian Simvastatin Survival Study (4S) were retrospectively evaluated to estimate the long-term relative risk for fatal and non-fatal myocardial infarction, sudden cardiac death and unstable angina associated with the MetSyn [54]. Post hoc results from these studies, after exclusion of patients with diabetes,
indicated that placebo-treated patients with MetSyn in AFCAPS/TexCAPS and 4S were, respectively, 1.4 (95% CI, 1.04–1.9) and 1.5 (95% CI, 1.2–1.8) times more likely to experience major coronary events than those without it [54]. Low HDL-C levels were associated with elevated risk for major coronary events in both studies. Patients with MetSyn showed increased risk for major coronary events irrespective of their Framingham-calculated 10-year risk score category (>20% vs ≤20%) [54]. Recently, the TNT study showed that high-dose aggressive therapy with atorvastatin in patients with coronary heart disease and MetSyn provides better protection from major cardiovascular events than the lower dose, irrespective of the presence of diabetes [55]. Besides their hypolipidaemic action, statins have several pleiotropic properties that may contribute to their clinical benefits [56]. Remarkably, it has been demonstrated that statins exert statistically significant blood pressure-lowering effects, particularly on systolic blood pressure [57,58].

Despite methodological problems of heterogeneity (e.g. primary vs secondary prevention, the type of statin used, placebo vs active controlled trials, the duration of follow-up and outcomes) the findings of a recent meta-analysis imply that statins are useful in the management of global vascular risk in subjects with hypertension [58]. Moreover, this influence seems to be more prominent in subjects with hypertension and is not related to the baseline value or the change in serum cholesterol during the treatment period [58].

The role of statins in renal protection is under intensive investigation since their presumed pleiotropic effects including anti-inflammatory, antifibrotic, antihypertensive and antioxidant could be clinically relevant in the prevention and progression of CKD [59,60]. In a recent meta-analysis it was demonstrated that statins reduce the rate of kidney function loss by 76% [60]. Another meta-analysis showed that statins significantly reduce albuminuria in microalbuminuric and macroalbuminuric patients but not in those with normal albumin levels (<30 mg/day) [61]. On the other hand, recent studies indicate that statin use may cause proteinuria, possibly by inhibition of protein uptake in proximal tubular cells [59,62]. Despite this apparent discrepancy, it has been proposed that processes related to tubular proteinuria are not implicated in the pathophysiology of renal function loss and therefore do not counteract the antiproteinuric effects of glomerular origin [59].

Consistent with this consideration, in a recent observational cohort study, statin use increased urine albumin excretion without a concomitant change in the GFR [63]. Nevertheless, contrary to previously published evidence [64], both the randomized controlled and the observational cohort part of this study pointed against a renoprotective effect of statins [63]. Collectively, it seems that statins provide a substantial benefit mainly in the progression of CKD, namely in patients who already have impaired renal function (GFR <60 ml/min/1.73 m²). Presumably, this is not necessarily the case in high-risk patients with multiple risk factors such as those with MetSyn. The GREACE study reported that renal function declines over a period of 3 years in dyslipidaemic coronary heart disease patients with normal or near normal renal function at baseline who were not treated with statin [65]. In addition, atorvastatin inhibited this deterioration and significantly increased GFR [65], whereas a post hoc analysis revealed that patients with MetSyn benefited more from this treatment [66]. Undoubtedly, larger prospective studies with longer follow-up periods are needed in order to elucidate the role statins in CKD prevention, especially in the setting of MetSyn.

Fibrates are hypolipidaemic drugs that act as PPAR-α ligands [67]. Apart from favourable effects on lipid parameters, mainly reduction of triglycerides and increase in HDL, they exert pleiotropic actions [67]. In other words, these agents have a potential in treating insulin resistance, dyslipidaemia, hypertension and in preventing diabetic nephropathy, inflammation and cardiovascular disease [68]. In this context, in the Diabetes Atherosclerosis Intervention Study (DAIS), it has been demonstrated that fenofibrate reduces the progression from normal albumin excretion to microalbuminuria in type 2 diabetic patients [69]. Although based on category analysis and not continuous data, a significant reduction in the progression of proteinuria in diabetic patients treated with fenofibrate was also described in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study [70]. On the other hand, fibrates, possibly with the exception of gemfibrozil, can cause a small though significant increase in serum creatinine levels [71]. The effect of these small serum creatinine elevations on long-term outcomes is under study. Finally, the role of fibrates in preventing CKD in patients with MetSyn and lipid abnormalities which may benefit from treatment with these agents (e.g. elevated triglycerides) is unknown and deserves further study.

**Drawbacks and Concerns**

Despite the aforementioned expectations regarding the multifactorial approach in MetSyn, some potential problems in the implementation of this strategy should be acknowledged. The adherence to intensified treatment, the side effects to polypharmacy, and the costs of multitarget therapies are the most prominent [30]. There is also a need to develop methodologies to identify MetSyn patients at high risk for CKD because these may receive the maximal benefits of such a therapy.

**Conclusions**

Patients with MetSyn are at increased risk for developing CKD while renal impairment further aggravates the existing cardiovascular risk. Thus, comprehensive
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and aggressive preventive care in these individuals is imperative. The intensified multifactorial approach could emerge as a promising strategy in high-risk patients. In line with this consideration, an increasing body of evidence suggests that treatments targeting specific components of MetSyn may favorably affect renal function. We therefore believe that the implementation of such a strategy in order to prevent CKD is feasible and worthwhile. Whether a multi-target therapy substantially modulates the development and progression of CKD in subjects with MetSyn remains to be elucidated. Finally, the relative value of specific drug treatments, diet, exercise and their different combinations, constitutes a subject for future research.

Conflict of interest statement. None declared.

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