Metabolic syndrome: a fata morgana?

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Metabolic syndrome: metabolic/medical complications of obesity

The criteria used to define the metabolic syndrome are increased waist circumference, increased triglycerides, decreased HDL-cholesterol, increased blood pressure and increased plasma glucose. According to the most widely used definition, the metabolic syndrome is diagnosed in persons who have three or more of these five abnormalities [1]. The history of the designation of the syndrome dates back to 1993, when it was stressed in the second report of the Adult Treatment Panel (ATP-II) of the National Cholesterol Education Program (NCEP), that the rising prevalence of obesity should be controlled from the perspective of prevention of cardiovascular (CV) disease [2]. Later, it was acknowledged that, despite recommendations, the problem of obesity had taken immense proportions, and that it would be a daunting task to treat every obese subject. In the third report of the Adult Treatment Panel (ATP-III) of the NCEP, in 2001, the metabolic syndrome was put forward with an intention of easing this task through putting emphasis on overweight and obese persons with evidence of medical complications [3]. Such persons would then deserve priority in clinical efforts to prevent the development of comorbidities of obesity through lifestyle changes, particularly weight reduction and increased physical activity.

Meanwhile, the metabolic syndrome has been exposed to vigorous critique [4,5]. The criteria have been found to be ambiguous and incomplete. It is uncertain whether insulin resistance is a unifying aetiology. The medical value of diagnosing the syndrome is unclear. Importantly, the most compelling point of the critique was that CV disease risk associated with the syndrome is not greater than the sum of its parts. Critics are even questioning whether the metabolic syndrome exists [5]. Others are vigorously arguing that the metabolic syndrome is of great value, and refute most allegations [3,6].

Is the metabolic syndrome useful for assessment of cardiovascular or renal risk?

Those who designated the metabolic syndrome in its current form had the intention of using it as an obesity counselling tool, rather than as a predictor of CV disease or diabetes [3]. If the syndrome was really intended as a predictor of CV risk, it would for instance not have been composed of continuous variables that are dichotomized, since it is well-known that dichotomization of continuous variables results in loss of predictive power of up to 35% [7,8]. The components of the metabolic syndrome, moreover, cluster with each other, implying that they are correlated. If correlated factors are used for the generation of prediction equations, one would expect them to take away part of each others relation with the outcome parameter, i.e. one would not expect them to be independent predictors. Established prediction equations, such as the ones derived from the Framingham study and the SCORE project, include several independent (almost) continuous variables, to take full advantage of their individual predictive properties [9–12]. Importantly, and in contrast to the metabolic syndrome, they invariably include age and current smoking as strong and independent risk factors. Thus, it is unlikely that the metabolic syndrome was defined to serve as a prediction equation.

Just to illustrate these principles, we have performed receiver operating characteristic (ROC) curve analyses for systolic blood pressure (SBP) (continuous variable), hypertension (dichotomized according to the ATP-III definition) and a recent Framingham equation (continuous variable) as predictors of the 496 CV events (CV mortality plus CV morbidity) that occurred during a median follow-up of 6.5 years in the 8217
of the 8952 people of the general population of the Groningen PREVEND study with full data available for analyses [11]. Figure 1 shows that the dichotomized variable hypertension [area under the ROC curve (AUCROC) 0.66 (95% CI 0.64–0.69)] is a significantly poorer predictor than the continuous variable SBP [AUCROC 0.73 (0.71–0.76)], with a calculated loss of predictive power of 30% (compared with no predictive value at all, i.e. an AUCROC of 0.50). It is also evident that the Framingham equation [AUCROC 0.81 (0.79–0.83)] performs significantly better than SBP alone. To also illustrate the consequences of dichotomization of the variables of the metabolic syndrome, we generated a prediction score using multivariable Cox-proportional hazard analysis with the continuous variables that define the metabolic syndrome (HDL-cholesterol, fasting glucose, triglycerides, SBP, and waist circumference), and performed a ROC curve analyses for the derived prediction equation (metabolic syndrome as continuous variable) vs the current dichotomized definition of the metabolic syndrome (Figure 2). To further illustrate how devastating it could be for a prediction equation to leave out age from the equation, we also performed a ROC curve analysis of age as a single continuous variable for prediction of CV events (Figure 2). The predictive value of the metabolic syndrome as a continuous variable [AUCROC 0.76 (0.74–0.78)] appears to be much better than that of the dichotomized metabolic syndrome [AUCROC 0.60 (0.57–0.62)]. Intriguingly, the predictive power of age alone [AUCROC 0.79 (0.77–0.81)] is still better than that of the metabolic syndrome as a continuous variable. A model in which all the aforementioned continuous variables of the metabolic syndrome were incorporated, together with age, current smoking and sex, reached an AUCROC of 0.83 (0.82–0.85), which was significantly better than the AUCROC of age alone (not shown in the figure). It should also be realized that the predictive power of the whole dichotomized metabolic syndrome is significantly lower that that of the continuous variable SBP alone, and also significantly lower than that of the dichotomized variable hypertension. Apparently, in the metabolic syndrome, the predictive power of the dichotomized variable hypertension is diluted by combining it with other, weaker, dichotomized predictors.

The overall conclusion that should be drawn is clear: the metabolic syndrome can in its current form not be of any particular use in the assessment of CV risk.

Is the concept of the metabolic syndrome then worthless?

The answer should be no. The metabolic syndrome created momentum for public and professional awareness about the enormous health hazards that are contained by the swelling waves of overweight, obesity and sedentary life style. The term metabolic syndrome also contains the notion that simple measures of overweight and obesity, such as body mass index (BMI), or even waist circumference, very imprecisely reflect the risk contained by the metabolic effects of an increased fat mass. The metabolic syndrome tries to ‘grasp’ this phenomenon, but can still not be considered more than a first attempt. Whether one judges this attempt as successful or not, depends on how one would like to measure success. If success were
judged by resolving a scientific problem, it would be judged very unsuccessful. However, if success were judged by gaining momentum in the public discussion, it would be considered very successful. It is in fact metabolic obesity without physical obesity for which the metabolic syndrome reached, but could not catch [13,14]. Concerning the health consequences of the rapidly evolving epidemic of obesity, it seems appropriate to take (abdominal) obesity itself into consideration, until a better proxy of ‘metabolic obesity’ comes available.

**What warnings does the obesity epidemic contain for kidneys and dialysis capacity?**

If the number of patients with end-stage renal disease (ESRD) is projected for the year 2015, ageing of the population and increasing prevalence of diabetes are accounted for, but not obesity [15]. It should further be realized that obesity does not cause disease, disability or death in an instant, but through an accumulated effect over years [16]. The much greater threat from obesity acquired at young age than obesity acquired during adulthood can be perceived easily from studies on life-expectancy. Once people have reached the age of 70, there is no noticeable effect of obesity on life-expectancy [17]. At the age of 40, however, there are appreciable losses of, on average, 7.1 years in obese female nonsmokers, and 5.8 years in their male counterparts [18]. Usually, the effect of obesity on mortality is grossly underestimated in studies that do not account for the negative effects of smoking and disability on body weight [19]. In a study in which the negative effect of smoking was not accounted for, it was found that obesity at the age of 20 years has an appreciably greater negative effect on life-expectancy than obesity at the age of 40 years [20]. A slow decrease with age, until the absence of an effect of obesity on life expectancy in the elderly, is consistent with progressive counterbalancing of increased risk associated with obesity in healthy subjects by a protective effect of obesity in subjects with chronic diseases. This opposite relationship between BMI and survival in patients with chronic diseases is known as the obesity paradox [21]. Apparently, once people have a chronic disease, such as coronary artery disease or heart failure, the fact that they are able to attain or acquire a high BMI despite this disease indicates that they are still equipped for survival. It should be realized that up to now studies on mortality risk associated with obesity were performed in populations in which the condition of obesity was commonly acquired during adulthood. However, the obese children and adolescents of today and tomorrow will be exposed to the physical and metabolic consequences of obesity for much longer periods of time [16]. It should be realized that as many as 80% of obese children become obese adults [22]. The quickly growing problem of childhood and adolescent obesity may therefore pose a much greater burden on health-care systems (and dialysis capacity) than currently foreseen [16,22,23]. A tsunami of childhood obesity is still out, but quickly approaching the coast.

**Medical complications of prolonged obesity**

Obesity does not only reduce life expectancy, it also induces disease and disability. Even beyond the age of 70, when there is no appreciable effect of obesity on life-expectancy, obese subjects are much more likely to become disabled, and to spend their remaining life in a disabled condition, than lean ones [17]. The complications of obesity are multiple, and include type 2 diabetes, hypertension, coronary heart disease, stroke, heart failure, venous thromboembolism, atrial fibrillation, osteoarthritis, cancer (breast, endometrium, colon, kidney), cholelithiasis, infertility, polycystic ovary syndrome and sleep apnoea [24–27]. The association of obesity with risk for diabetes is most notable. Women aged 30–55 years with a BMI ≥35 kg/m² have, for instance, a more than 80-fold increase in risk, and men of this degree of obesity a more than 40-fold increase [28,29].

**Obesity-related renal disease**

Until recently, obesity per se was not acknowledged as an important risk factor for ESRD. Extensive reviews on obesity and its complications have not mentioned it as a possible complication [24,30]. Previous prospective studies that investigated obesity as a risk factor for development of ESRD required it to be independent of diabetes and hypertension, because diabetes and hypertension are established risk factors for ESRD (Figure 3, upper panel) [31–33]. In our opinion, such a way of analysing is inappropriate, since obesity is a risk factor for—and a cause of—diabetes and hypertension, which then, in turn, may cause ESRD. Only one contemporary study did not inappropriately adjust for diabetes and hypertension, and did not require the risk contained by obesity to be independent of diabetes and hypertension [34]. In this by far largest study, with a total of 1471 cases of ESRD during 834 7955 person-years of observation, diabetes and hypertension were correctly considered as possible intermediate variables in the pathway between increased BMI and ESRD (Figure 3, lower panel) [34]. A graded relationship between classes of obesity and risk of development of ESRD was identified. In the overall population, the hazard ratio was seven when subjects with severe obesity (BMI ≥40 kg/m²) were compared with subjects with normal weight (BMI 18.5–24.9 kg/m²). This hazard ratio decreased to five after adjustment for diabetes and hypertension, indicating that obesity may also lead to renal failure through other pathways...
in a huge number of obese subjects at risk for more chronic complications of obesity, such as renal failure. The obesity paradox should also seriously be considered as a potential switch between the competing risks of ESRD and death, because the risk for reaching ESRD (rather than death) seems to be considerably higher in obese people with age <40 years than in obese people with age ≥40 years [34].

It should be realized that it takes time for obesity to let its malicious effects manifest in disease and disability [16]. Even induction of type 2 diabetes, for instance, remains hidden for prolonged periods of time behind a curtain of compensatory increase in pancreatic β-cell mass [36]. This compensatory expansion of β-cell mass allows for increased insulin production, which is necessary for maintenance of euglycaemia in the perspective of existing insulin resistance [37]. In humans, both increased β-cell replication and neogenesis seem to play a role in this adaptation [38]. Once these resources of new β-cells become exhausted, and cannot meet with continued—and possibly increased—β-cell death, β-cell mass declines, and type 2 diabetes ensues [36]. The same seems to be true for renal disease. The kidneys appear to adapt to the increased metabolic load of obesity with an increase in size [39,40]. At the same time, there is an increase in glomerular filtration and an increased tendency for albuminuria [41]. A likely scenario for the decline in renal function associated with obesity is that, analogous to the decline in β-cell function, renal function starts to decline once renal reserve capacity becomes exhausted, and further hyperfiltration in the remaining glomeruli results in increasing albuminuria and a more rapid decline in renal function.

Some people may have very susceptible pancreatic β-cells, and develop diabetes so early in the course of obesity, that the newly developed diabetes can still induce additional diabetes-related renal hyperfiltration on top of the effects of obesity, while others, with extremely susceptible kidneys, e.g. kidneys that have already been damaged by another hit or kidneys with a congenitally low nephron number, may develop ESRD be pancreatic β-cells decompensate [42]. The high prevalence of type 2 diabetes compared with ESRD suggests that obesity more easily “burns-off” pancreatic β-cells—and probably also vasculature—than kidneys. An epidemic of ESRD riding on the tide of childhood and adolescent obesity may therefore be expected to lag one or two decades behind an epidemic of type 2 diabetes. The impact of childhood obesity on development of diabetes is already so high that type 2 diabetes is quickly taking over from type 1 as the most common type of diabetes diagnosed in children [43]. With the rapidly evolving epidemic of childhood obesity, number of people who have ‘burned-off’ their kidneys long before the status of the vasculature is no longer compatible with survival may be far greater than any opportunistic prediction could foresee.

Fig. 3. (Upper panel) Classic vs (lower panel) contemporary view on the relation between obesity and development of end-stage renal disease (ESRD). In the contemporary view, it requires further clarification whether and how obesity can accelerate development of ESRD independent of diabetes and hypertension.

Potential impact of an obesity paradox on incidence of ESRD

Currently, patients with CKD are 5–10 times more likely to die than to reach ESRD [15]. In the aforementioned prospective study on obesity as a risk factor for development of ESRD, 1471 cases of ESRD were observed, compared with 56,336 deaths [34]. Only a small shift in chances between reaching ESRD and death will therefore have a huge impact on the incidence of ESRD. In case the CV mortality risk of obesity in the future is decreased by, for instance, 30% by preventive measures and intervention, which does not seem unlikely, this will result
Implications of the metabolic syndrome for the management of renal patients

The existence of an obesity paradox suggests that implications of the metabolic syndrome for the management of patients with established renal disease will be low. A recent study indicates that this could even be contradictory to traditional expectations, if application of the concept would lead to advice for weight loss. In this recent study, the well-known fact that unintentional weight loss is a risk factor for mortality was corroborated [44]. Intentional weight loss, however, also appeared to be a risk factor for death if it was initiated once ill health was established [44]. The benefit of intentional weight loss was only present in relatively young, markedly overweight, still healthy subjects. It is currently too early to state how management should be, but it could well be that individual risk factors, such as high blood pressure and diabetes, should be treated, whereas obesity, even if it is underlying, should be untouched.

The recent fire ignited under the appraisal and acknowledgement of obesity and the associated metabolic syndrome as cause and risk factors of chronic kidney disease and ESRD will, however, be of great importance for the management of patients at risk for development of these diseases. It has, for instance, caused people to realize that diabetes and hypertension are consequences of obesity, and that it is, to a great extent, obesity which drives epidemics of ESRD that previously have been attributed to diabetes and hypertension. It is clear that obesity is the first risk factor that should be tackled, and that hypertension and diabetes are only secondary ones. If we do not succeed in tackling the rapidly growing problem of childhood and adolescent obesity at an early age, an unpredicted shortage in dialysis facilities and equipment could become a reality.

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References

Ultrapure dialysis fluid—how pure is it and do we need it?

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The issue

Originally a definition of water quality for the semiconductor industry, the term ‘ultrapure’ has been adopted by the dialysis community. The discussion has developed from basic definitions and methods for quantification to clinical benefits and recommendations for implementation. Today, ultrapure dialysis fluid is subject to the demands of evidence-based medicine or at least evidence-based cost-effectiveness. The sequence from growing awareness to widespread conviction and practical implementation of ultrapure dialysis fluid is similar to the process for biocompatible dialysis membranes some 10–15 years ago. So, where do we stand with regard to ultrapure dialysis fluid?

What is ultrapure?

The term ‘ultrapure’ started to appear in dialysis literature in the early 90s and it meant that the fluid was highly purified in comparison to standard procedures [1]. The fluid appeared to be free from bacteria and endotoxin when routine methodology was used for testing. One millilitre of water or dialysis fluid spread on a suitable agar plate or tested for endotoxin showed neither growth nor activity. Some people misunderstood this and reference to ‘sterile dialysate’ was heard, although the fluid was far from sterile according to the definitions of the pharmacopoeia [2,3]. Ultrapure was later defined as containing <0.1 colony forming unit/ml (CFU/ml) using sensitive assays and <0.03 endotoxin unit/ml (EU/ml), the latter being the sensitivity level for the simplest of the Limulus Amoebocyte Lysate (LAL) assays, the gel clot test [4]. This definition is now widely accepted and referred to in clinical guidelines [5] as well as national