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Obesity and hypertension—the issue is more complex than we thought

Krzysztof Narkiewicz

Department of Hypertension and Diabetology, Medical University of Gdańsk, Gdańsk, Poland

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'That which does not kill you, makes you stronger'—Friedrich Nietzsche

Introduction

The relevance of both hypertension and obesity, as important public health challenges, is increasing worldwide. Compared with the year 2000, the number of adults with hypertension is predicted to increase by ~60% to a total of 1.56 billion by the year 2025 [1]. The growing prevalence of obesity is increasingly recognized as one of the most important risk factors for the development of hypertension. This epidemic of obesity and obesity-related hypertension is paralleled by an alarming increase in the incidence of diabetes mellitus and chronic kidney disease.

This editorial examines the evidence linking obesity with hypertension, reviews the mechanisms underlying this link, and discusses its potential implications for renal disease. Earlier studies attributed the link between obesity and hypertension primarily to haemodynamic factors. Recent evidence indicates that the association is much more complex than initially thought.

Good weight and measure are heaven's treasure

Excess body weight is the sixth most important risk factor contributing to the overall burden of disease worldwide [2]. More than 1 billion adults and 10% of children are now classified as overweight or obese [2]. In the USA, obesity is set to overtake smoking in 2005 as the main preventable cause of illness and premature death [3].

Correspondence and offprint requests to: Krzysztof Narkiewicz, MD, PhD, Department of Hypertension and Diabetology, Medical University of Gdańsk, Debinki 7c, 80-952 Gdańsk, Poland.
Email: knark@amg.gda.pl

Obesity and in particular central obesity have been consistently associated with hypertension and increased cardiovascular risk. Based on population studies, risk estimates indicate that at least two-thirds of the prevalence of hypertension can be directly attributed to obesity [4]. Apart from hypertension, abdominal adiposity has also been implicated in the pathogenesis of coronary artery disease, sleep apnoea, stroke and congestive heart failure [2].

There is increasing evidence that obesity contributes to the development as well as to the progression of chronic kidney disease [5]. Obesity may cause glomerular hyperfiltration, increased urinary albumin loss and progressive loss of renal function caused by focal segmental glomerulosclerosis [6,7]. In patients with established renal disease, obesity accelerates progression [8,9]. The importance of obesity in causing renal damage has recently been emphasized by population-based studies in apparently healthy subjects. First, multivariate analysis of the data of the PREVEND study showed that the body mass index is independently associated with urinary albumin excretion and that this relationship is closer in males than in females [5] (Figure 1). The relationship between body mass index and impairment of renal function is evident even in subjects without overt obesity [10]. Secondly, in the general population, obesity is associated with an increased incidence of chronic kidney disease [11] and end-stage renal failure [12].

Given the close link between obesity and cardiovascular disease, it has been suggested that current trends in obesity might lead to a decline of the life expectancy in the USA in the 21st century [13]. Similar trends are likely to occur in other countries.

Still waters run deep

Obesity-related metabolic abnormalities and impairment of cardiovascular function may be present even at a young age, and progress asymptomatically for decades before clinical manifestations set in. It is conceivable that these early abnormalities found in young obese subjects might facilitate the future development of hypertension and atherosclerosis

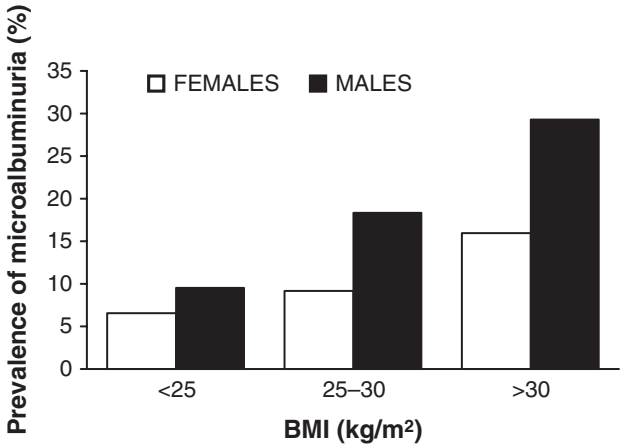

Fig. 1. Prevalence of microalbuminuria according to body mass index in the PREVEND study (modified from [5]).

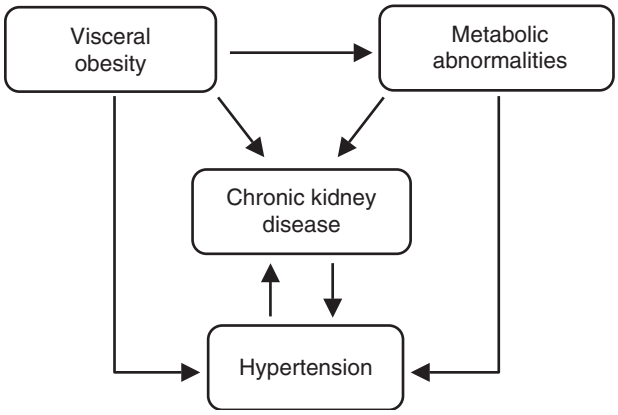

Fig. 2. Potential mechanisms linking obesity, hypertension and chronic kidney disease.

independently of other traditional risk factors. This hypothesis is supported by recent findings which link obesity to accelerated progression of coronary artery calcification as a marker of atherosclerosis in apparently healthy individuals with an otherwise favourable cardiovascular risk profile [14].

The precise mechanisms linking obesity to hypertension and increased cardiovascular risk are not fully understood. However, neuroendocrine mechanisms and, most recently, factors derived from adipose are thought to play a major role [15,16]. Obesity might lead to hypertension and cardiovascular disease by activating the renin–angiotensin–aldosterone system, by increasing sympathetic activity, by promoting insulin resistance and leptin resistance, by increased procoagulatory activity and by endothelial dysfunction. Further mechanisms include increased renal sodium reabsorption, causing a shift to the right of the pressure–natriuresis relationship and resulting in volume expansion [17]. Obstructive sleep apnoea may importantly contribute to sympathetic activation in obesity. Finally, obesity may increase cardiovascular risk through subclinical inflammation.

Obesity-related hypertension is commonly associated with further elements of the metabolic syndrome, such as insulin resistance and glucose intolerance. In particular, one should be aware that diabetes *de novo* occurs in 2% of treated hypertensive patients per year [18]. Furthermore, new onset diabetes increases the cardiovascular risk. The adverse impact of newly diagnosed diabetes is similar to that of known diabetes. There are compelling arguments for the concept that metabolic abnormalities associated with obesity not only play an important role in pathogenesis of cardiovascular disease, but also contribute to different types of renal injury. Tubular injury, as the first sign of renal damage in hypertension, is closely linked to metabolic disturbances [19]. Kincaid-Smith [20] recently proposed that obesity and the insulin resistance syndrome play a major role in the genesis of renal failure in hypertensive patients by what conventionally had been labelled 'hypertensive nephrosclerosis'.

It takes two to tango

Obesity is associated with an increased risk of cardiovascular disease, but this requires that obesity is combined with hypertension. In overweight and obese subjects, the cardiovascular risk is not significantly increased unless hypertension is present [21]. This observation underscores the role of hypertension as a mediator through which obesity may cause cardiovascular disease.

While obese subjects are prone to hypertension, hypertensive subjects also appear to be prone to weight gain. Both the Framingham and Tecumseh studies have shown that future weight gain is significantly greater in hypertensive patients than in normotensive subjects, suggesting that even normal weight hypertensives are at a high risk of developing obesity [22]. Therefore, the relationship between obesity and hypertension might be described as a 'two-way street' [22], implying individual susceptibility to both conditions or common environmental factors.

A chain is not stronger than its weakest link

It is clear that obesity-related hypertension is a multifactorial disorder. At this time, it is not possible to identify one single mechanism as the dominant aetiological factor. Genesis and evolution of obesity-related co-morbidity presumably depend on several genetic and environmental factors. It is likely that obesity, hypertension and metabolic abnormalities interact and potentiate their individual impact on cardiovascular risk (Figure 2). In this context, renal factors may have a decisive influence. The number of nephrons is reduced in patients with primary hypertension [23]. In these patients, obesity may confer an increased risk of chronic kidney disease, especially when additional factors, such as diabetes or lipid abnormalities, are superimposed. Structural damage of the kidneys may further increase blood pressure and predispose to cardiovascular events.

It is tempting to speculate that the clinical course and the prognosis of a given patient depend on the weakest link in the chain comprising obesity, hypertension and metabolic abnormalities. It is possible that distinct subgroups of obese subjects are prone to an early increase in blood pressure, an early onset of diabetes or an early onset of chronic kidney disease.

Think globally, act globally

There is a clear need to develop a global strategy for managing the increasing number of overweight and obese subjects in the community. Obesity, as a major contributor to global cardiovascular risk, requires coherent management [2]. Effective long-term weight loss necessitates persistent changes in dietary quality, energy intake and physical activity [2]. Weight loss is associated with a significant reduction of blood pressure and has beneficial effects on the associated risk factors.

Even modest reduction in body weight can cause a meaningful reduction in the activity of the renin–angiotensin–aldosterone systems in the circulation and in adipose tissue which makes a major contribution to the blood pressure decrease. Weight loss of 5% is associated with the reduction of angiotensinogen levels by −27%, renin by −43%, aldosterone by −31%, angiotensin-converting enzyme activity by −12% and angiotensinogen expression by −20% in adipose tissue [24].

Furthermore, weight loss has been shown to improve endothelial function [25], decrease sympathetic nerve activity [26] and improve baroreflex function [26]. Animal studies indicate that weight loss decreases proteinuria and might even reverse morphological signs of renal damage [27]. This repair of renal injury is independent of blood pressure control. Whether weight loss, induced by either lifestyle changes or pharmacotherapy, is also associated with a reduced number of cardiovascular events remains to be determined.

Every rule has its exception

Cardiovascular risk factors including obesity are more prevalent in patients with end-stage renal disease than in age-matched controls [28]. However, there is growing evidence that the relationship between body mass index, nutritional state and cardiovascular risk profile might be different in renal patients compared with the general population [29,30] (Figure 3). Obesity has been shown paradoxically to enhance survival of patients undergoing haemodialysis. This phenomenon is called reverse epidemiology, risk factor reversal or altered risk factor pattern [29].

Several mechanisms have been postulated as potential causes of or explanations for the phenomenon of reverse epidemiology in patients undergoing haemodialysis. These include the malnutrition inflammation complex syndrome, alterations in circulating cytokines, unique neurohormonal constellations, endotoxin–lipoprotein interaction, reverse causality, survival bias and time discrepancies among competitive risk factors [29]. It is not clear whether these mechanisms are specific for renal patients, as other conditions such as congestive heart failure, advanced age and malignancy are also associated with risk factor reversal. Nevertheless, these findings raise the question of whether obese patients undergoing haemodialysis should be advised to lose weight.

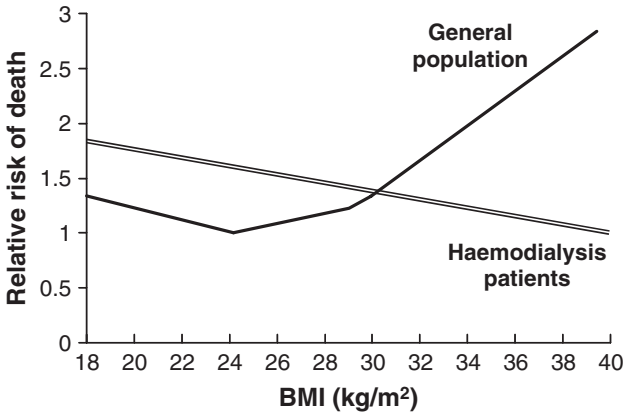

Fig. 3. Comparison between the effects of body mass index on all-cause mortality in the general population and in maintenance haemodialysis patients (modified from [29]).

Interestingly, reverse epidemiology is not observed in patients treated with peritoneal dialysis. In this group of patients, obesity is a significant risk factor for death and technique failure [31].

Conclusions

Obesity is an independent risk factor for the development and progression of hypertension, cardiovascular disease and chronic kidney disease. There is growing evidence that obesity and associated metabolic abnormalities may induce and accelerate renal complications in essential hypertension. The clustering of obesity and other features of the metabolic syndrome might have important implications for prevention, particularly with regard to whether interventions targeted at visceral obesity would have beneficial effects on cardiovascular and renal morbidity.

Obesity paradoxically appears to be a survival factor in patients with end-stage kidney failure undergoing haemodialysis. The impact of weight changes on prognosis in these patients is potentially of relevance when devising future treatment strategies for chronic renal failure and its cardiovascular consequences.

Conflict of interest statement. The author has received personal consultancies, honoraria or travel support from conference organizers for individual lectures on obesity from Abbott, Roche and Sanofi-Aventis.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005; 365: 217–223
2. Haslam DW, James WP. Obesity. *Lancet* 2005; 366: 1197–1209
3. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *J Am Med Assoc* 2004; 291: 1238–1245
4. Krause RM, Winston M, Fletcher BJ, Grundy SM. Obesity. Impact on cardiovascular disease. *Circulation* 1998; 98: 1472–1476
5. de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL. PREVEND study group. Obesity and target organ damage: the kidney. *Int J Obes Relat Metab Disord* 2002; 26 [Suppl 4]: S21–S24
6. Kambham N, Markowitz GS, Valeri AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int* 2001; 59: 1498–1509
7. Ribstein J, du Cailar G, Mimran A. Combined renal effects of overweight and hypertension. *Hypertension* 1995; 26: 610–615
8. Praga M, Hernandez E, Herrero JC *et al*. Influence of obesity on the appearance of proteinuria and renal insufficiency after unilateral nephrectomy. *Kidney Int* 2000; 58: 2111–2118
9. Bonnet F, Deprele C, Sassolas A *et al*. Excessive body weight as a new independent risk factor for clinical and pathological progression in primary IgA nephritis. *Am J Kidney Dis* 2001; 37: 720–727
10. Bosma RJ, Homan van der Heide JJ, Oosterop EJ, De Jong PE, Navis GJ. Body mass index is associated with altered renal hemodynamics in non-obese healthy subjects. *Kidney Int* 2004; 65: 259–265
11. Kramer H, Luke A, Bidani A, Cao G, Cooper R, McGee D. Obesity and prevalent and incident CKD: the hypertension detection and follow-up program. *Am J Kidney Dis* 2005; 46: 587–594
12. Esiki K, Ikemiya Y, Kinjo K, Inoue T, Esiki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. *Kidney Int* 2004; 65: 1870–1876
13. Olshansky SJ, Passaro DJ, Hershow RC *et al*. A potential decline in life expectancy in the United States in the 21st century. *N Engl J Med* 2005; 352: 1138–1145
14. Cassidy AE, Bielak LF, Zhou Y *et al*. Progression of subclinial coronary atherosclerosis. Does obesity make a difference? *Circulation* 2005; 111: 1877–1882
15. Engeli S, Sharma AM. Role of adipose tissue for cardiovascular–renal regulation in health and disease. *Horm Metab Res* 2000; 32: 485–499
16. Wiecek A, Kokot F, Chudek J, Adamczak M. The adipose tissue—a novel endocrine organ of interest to the nephrologist. *Nephrol Dial Transplant* 2002; 17: 191–195
17. Wofford MR, Hall JE. Pathophysiology and treatment of obesity hypertension. *Curr Pharm Des* 2004; 10: 3621–3637
18. Verdecchia P, Reboldi G, Angeli F *et al*. Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension* 2004; 43: 963–969
19. Tylicki L, Rutkowski B. Metabolic disturbances as strong determinator of kidney injury in essential hypertension. *J Hypertens* 2005; 23: 1433–1434
20. Kincaid-Smith P. Hypothesis: obesity and the insulin resistance syndrome play a major role in end-stage renal failure attributed to hypertension and labelled 'hypertensive nephrosclerosis'. *J Hypertens* 2004; 22: 1051–1055
21. Thomas F, Bean K, Pannier B, Oppert JM, Guize L, Benetos A. Cardiovascular mortality in overweight subjects: the key role of associated risk factors. *Hypertension* 2005; 46: 654–659
22. Julius S, Valentini M, Palatini P. Overweight and hypertension: a 2-way street? *Hypertension* 2000; 35: 807–813
23. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron number in patients with primary hypertension. *N Engl J Med* 2003; 348: 101–108
24. Engeli S, Bohnke J, Gorzelniak K *et al*. Weight loss and the renin–angiotensin–aldosterone system. *Hypertension* 2005; 45: 356–362
25. Ziccardi P, Nappo F, Giugliano G *et al*. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. *Circulation* 2002; 105: 804–809
26. Grassi G, Seravalle G, Colombo M *et al*. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. *Circulation* 1998; 97: 2037–2042
27. Nangaku M, Izuhara Y, Usuda N *et al*. In a type 2 diabetic nephropathy rat model, the improvement of obesity by a low calorie diet reduces oxidative/carbonyl stress and prevents diabetic nephropathy. *Nephrol Dial Transplant* 2005; 20: 2661–2669
28. Longenecker JC, Coresh J, Powe NR *et al*. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE study. *J Am Soc Nephrol* 2002; 13: 1918–1927
29. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. *Am J Clin Nutr* 2005; 81: 543–554
30. Kopple JD. The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. *Am J Clin Nutr* 2005; 81: 1257–1266
31. McDonald S, Collins JF, Johnson DW. Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. *J Am Soc Nephrol* 2003; 14: 2484–2901

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