Proteinuria as a predictor of risk for cardiovascular disease – a new insight

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Abstract: Mortality and morbidity due to cardiovascular disease is one of the fundamental health problems at present. Proteinuria is not only commonly recognized factor of progression of chronic renal diseases, but is also independent risk factor for cardiovascular complications. Lately, the value of albuminuria as a prognostic factor in the course of cardiovascular diseases has increased its significance. Not long ago, there was considered that only microalbuminuria (quantity of excreted albumins in urine above 30 to 300 mg daily) indicates on increased risk of complications of such diseases as arterial hypertension or diabetes. However, observational studies as well as interventional studies lead us to verify that view. It turned out that in the general population the number of cardiovascular complications leading to death increases in proportion to the quantity of albumins excreted in urine. Moreover, it was found that the relationship is continuous in a wide range of albuminuria even at value below the lower limits accepted now as normal levels, i.e., 30 mg per day corresponding with urinary albumin concentration 20 mg/l. It means that not only the quantity of excreted albumins but also the presence of albumin in urine indicate a higher risk of cardiovascular death. It may be assumed therefore that the presence of albumin in urine gives the evidence of unfavorable functional state of the circulatory system followed by fatal consequences. Therefore, the presence of albuminuria ought to be considered in quality and quantity aspects.

Key words: albuminuria, proteinuria, risk of cardio-vascular disease, uric acid

Mortality and morbidity due to cardiovascular system diseases are currently counted among fundamental health problems. Population studies demonstrate that the so called "traditional risk factors" constitute the basis for cardiovascular system diseases [1]. Among these factors are lipid disturbances, left ventricle hypertrophy, male sex, and others. On the other hand, irrespective of the cited above commonly known risk factors for cardiovascular complications, it was also stated that chronic kidney disease is the independent risk factor in mortality and morbidity due to cardiovascular causes [2,3]. Chronic kidney disease is described as kidney injury persisting ≥3 months, defined as the presence of structural or functional kidney abnormality with normal or lower glomerular filtration rate (GFR), what is manifested by morfological abnormality or markers of renal injury and abnormality in blood and urine composition or abnormal results of clinical picture. The other element of definition of chronic kidney disease is GFR ≤60 ml/min/1.73 m^2 during ≥ 3 months, with or without kidney injuries [4]. In addition, it was found that any lowering of GFR about 5 ml/min/1.73 m^2 is associated with the increase of about 26% in mortality due to cardiovascular causes [5]. These facts suggested that increased mortality in patients with chronic kidney disease is caused by the mentioned above "traditional risk factors". In fact, further cross-sectional studies allowed establishing the relation between glomerular filtration rate and proteinuria versus "traditional risk factors" for cardiovascular diseases [6,7]. The findings of these studies showed, among others, the negative correlation between glomerular filtration rate and systolic hypertension value and triglyceride level, and the positive correlation between GFR and the level of high-density lipoprotein (HDL) cholesterol fraction. A similar relation was found between the extent of proteinuria and the level of serum lipide and blood arterial pressure value [6]. Therefore, it initially seemed that the increased mortality in patients with chronic kidney diseases resulted from an interaction with "traditional risk factors". However, the in-depth analysis of obtained results did not show such an obvious relation between the risk factors and cardiovascular complications in patients with chronic kidney diseases. When the Framingham assessment method [coronary point score] was employed in the studies, the results showed that the "traditional risk factors" were only in a minimal degree responsible for the evident increase in mortality in patients with chronic kidney diseases [6]. Based on these findings the assumption was made that high mortality among chronic kidney disease patients might depend on other factors than the "traditional risk factors" [8].

It is supposed that so called "non traditional" risk factors, named also the "connected with renal insufficiency factors"

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are the main causes of increased cardiovascular morbidity and mortality in patients with chronic renal diseases. Among them are: anemia, chronic inflammatory state, hyperhomocysteinemia, disturbances of calcium-phosphate balance, and undernutrition [8]. The prospective study called CRIC is currently being carried out with the aim of determining the contribution of traditional or nontraditional risk factors to cardiovascular complications in patients with chronic renal insufficiency [9].

Irrespective of the cited above study and views, a reasonable assumption can be made that the frequency of cardiovascular complications in patients with chronic renal diseases may be decreased through the counteracting or restraining the progression of chronic kidney diseases [10]. One of the most significant, apart from arterial hypertension, factors which undesirably influence the progress of renal diseases is proteinuria [10,11]. Proteinuria is not only a commonly recognized factor for the progression of chronic renal diseases, but it is also an independent risk factor for the appearance of cardiovascular complications. It ought to be stressed that the occurrence of cardiovascular complications has been a health problem known since a long time ago. The study named RENAAL demonstrated a particular relationship between the proteinuria stage and the progression of chronic renal diseases and cardiovascular complications. The study showed that the decrease in albumin excretion in urine after losartane therapy was associated with the lower frequency of cardiovascular complications [12].

Lately, the diagnostic value of microalbuminuria as a prognostic factor in the cause of cardiovascular diseases has gained in importance. Until recently, it has been thought that only microalbuminuria, i.e., the amount of excreted albumins in urine above 30 to 300 mg per a day indicates to the increased risk for complications in the course of some pathological symptoms, e.g. arterial hypertension or diabetes [13,14]. However, the results of observation and intervention studies show that this view should be verified. They demonstrate that in the total population the number of cardiovascular complications leading to death increases proportionally to the quantity of albumins excreted in urine [15]. Moreover, it was found that this relationship is continuous in a wide range of albuminuria levels, even at the accepted till now as normal values below the bottom limits, i.e., 30 mg per a day corresponding with 20 mg albumin level in 1 l urine. This prospective study found that the number of cardiovascular incidents rose gradually already in the range of albuminuria from 0 to 20 mg/l previously assumed as a normal state. It means that not only the quantity of excreted albumins, but also the presence of albumin in urine indicate to a higher risk of cardiovascular death [15]. It may be assumed therefore that the presence of albumin in urine is the evidence of an unfavorable functional state of circulatory system followed by fatal consequences. Therefore, the presence of albuminuria ought to be considered in quality and quantity aspects. The next prospective study also questioned the adopted albuminuria limits and showed that the number of cardiovascular complications increased significantly when the quantity of excreted albumins with urine exceeded 4.8 μg/min, which corresponds to about 6 mg/l [16,17]. It may be stressed that at this level the albuminuria was an independent risk factor not only in chronic renal disease [16]. Similar findings were presented many years ago by Australian scientists who found increased blood systolic tension and lower plasma HDL level in a group of healthy people with albuminaria higher than 5.3 mg/l [18]. It should be stressed that in this study statistically significant differences in systolic blood pressure referred to values considered till now as a normal range, i.e., 113.1 mmHg at albuminuria <5.3 mg/l and 115.2 mmHg at albuminuria >5.3 mg/l. The relations similar to the described above relationship between albuminuria level (from normo- to microalbuminuria) and changes in the vessel wall structure were found in different diseases, including arterial hypertension [19].

Interventional studies provide additional evidence indicating to the prognostic importance of albuminuria in the case of cardiovascular complications development. One of them demonstrated that therapy with fosinopril decreased by 40% cardiovascular complications and at the same time albumin excretion was decreased by about 26% [20]. Favorable effects of that drug group are commonly known. It is an interesting fact that the cited study included patients in which, before treatment, albumin excretion was within the limits from 15.8 to 41.3 mg/d [20]. This suggest that drugs affecting the function of renin-angiotensin-aldosterone system may be beneficial also for patients with even minimally expressed albuminuria [20]. Moreover, the study which assessed the effect of losartane on albuminuria level in connection with the risk for cardiovascular complications, showed that the decrease of albuminuria by 50% was associated with the decreased by 27% risk for health failure [12].

It is commonly thought that albuminuria is the expression of endothelial functional failure [21]. However, available data indicate that failure of endothelial function occurs much earlier than albuminuria [22,23]. It means that the activity of one ore more factors results in functional endothelial disorders followed by microalbuminuria. It may be assumed that albuminuria is a consequence of early appearing changes in endothelium activity. These changes are the basis for the total circulatory system lesions development [24]. It is then most probable that pathological processes leading to the development of atherosclerosis within the cardiovascular system take place before the appearance of albuminuria [25]. Thus, it can be assumed that at the moment of albuminuria manifestation, irrespectively of its size, atherosclerotic changes in the cardiovascular system are already developed in a patient.

This suggests that patients with even the early stage albuminuria are a high risk group for cardiovascular complications. The appearance of albuminuria may indicate that factors undesirably affecting endothelium function might have acted earlier, long before the manifestation of albuminuria. Currently, among the factors undesirably affecting endothelium function a chronic inflammatory state is often mentioned. It is probably caused by commonly known metabolic disturbances that accompany arterial hypertension or diabetes [25-27]. It should be stressed that the inflammatory state is an extremely dynamic process which intensifies during the course of the disease and

leads to more and more advanced and unfavorable changes within the vessels [25]. The changes in the activity of inflammatory processes during the duration of the disease may explain the fact that the frequency of cardiovascular complications increases proportionally to the duration of the disease. It is also thought that prothrombus factors which activity increases in the course of the inflammatory process play a significant role in the progression of atherosclerosis [25,28].

Interesting is the fact that microalbuminuria occurs also in 3% of the healthy population with correct blood pressure and glycemia. Microalbuminuria is however accompanied by an inflammatory state and insulin resistance. Therefore, it can not be excluded that some mechanisms responsible for the appearance of microalbuminuria are common for people with normal blood pressure and those with hypertension or with type 2 diabetes mellitus [29].

Among many metabolism disturbances associated with hypertension or diabetes is hyperuricemia, a factor favoring the progress of chronic inflammatory state, which results in the impairment of endothelial function. Currently, more and more attention is paid to the role of this factor, because it was found that the uric acid level is also a factor modifying the response of endothelium to pharmacological vasodilatation drugs, e.g. acetylcholine. The studies showed that the decreased due to the allopurinolum effect uric acid level led to higher dilatation of vessels influenced by acetylcholine than it was observed before the administration of xantine oxidase inhibitor [30]. Hence, it may be assumed that uric acid is one of the factors which may play a significant role in the process of endothelium impairment and ultimately cause atherosclerosis. This is why in the light of current opinions more and more attention is paid to the purine aberrations which therapy is the prevention of cardiovascular system and kidney complications [30].

This problem deserves more attention also because hyperuricemia can be treated with drugs other than xantine oxidase inhibitors. Here the beneficial uricosuric properties of losartane should be stressed. This drug has an established position in the therapy of arterial hypertension, diabetic nephropathy during the progress of type 2 diabetes mellitus, and cardiovascular system diseases, because it retards the activity of renin-angiotensin-aldosterone system [31]. Apart from its beneficial effect on renin-angiotensin-aldosterone system, the drug possesses significant uricosuric properties causing the decrease in uric acid level in plasma of patients with arterial hypertension, as well as in patients receiving thiazide [32,33]. Moreover, it should be emphasized that losartane, by increasing the excretion of uric acid in urine, lowers the risk of uric acid concernments precipitation in urine, because its concomitant quality is alkalization of urine. As it was pointed out earlier, microalbuminuria is considered as an exponent of impaired endothelial function. On the other hand, it should be taken into consideration that microalbuminuria is only a substitute for the index designating the functional state and failure of endothelium. There are some reasons for that. Firstly, albuminuria, i.e., the quantity of albumin excreted in urine, is the effect of several local factors acting within the nephron. It depends, not only directly, on the changes in glomerule vessel loop pressure concomitant with arterial hypertension [34,35]. Moreover, the value of excreted albumin in urine also depends on the state of renal tubules, the function of which may be disturbed in consequence of arterial hypertension, or secondarily to vessel changes within the tubular-intestitial tissue [36]. Even if we accept a far-reaching simplification that albuminuria is solely the expression of endothelial function failure within the renal glomerule, it does not mean that similar in respect of quality and quantity changes may occur in other parts of the cardiovascular system [24,37]. Daily clinical observations clearly indicate that both the progress and type of vessel complications are different in patients with the same disease. With all the presented here various limitations resulting from the mechanisms leading to the development of albuminuria, from the clinical point of view it still remains an important prognostic indicator for the appearance of cardiovascular complications.

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