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EDITORIAL

Reverse epidemiology in hemodialysis patients. Lessons from Japanese registries

Épidémiologie paradoxale (inversée) chez les patients hémodialysés. Leçons tirées de registres japonais

Introduction

It is well known that hemodialysis patients are at an increased risk of death from cardiovascular disease (CVD) as shown by relative risk of 10–30 [1] as compared with the general population. What should we do to reduce the risk of CVD death? Cholesterol lowering? Weight reduction? However, Degoulet et al. [2] reported in 1982 that higher total cholesterol and higher body mass index (BMI) were both predictors of better survival in an observational cohort of French hemodialysis patients. The same was true when CVD death was taken as an alternative endpoint. Similar data have been reported for dialysis patients in the US and Japan. The strange relationship between risk factors and mortality is called ''cholesterol paradox'', ''obesity paradox'' or ''reverse epidemiology'' in hemodialysis patients. This topic has gained much attention in a view that this is not the matter only for the dialysis population, but rather an important issue for public health [3]. Here, we present some important observations from Japan and propose a hypothesis with regard to mechanisms for the reverse epidemiology.

Risk of CVD event occurrence and risk of fatality

The relative risk of death from CVD in hemodialysis patients is 10–30 as compared with the general population in Europe and the US [1]. Similar figures can be calculated for Japanese patients. But this does not indicate that hemodialysis patients experience 10 to 30 times more CVD events than the general population. Based on the report of the registry data in Okinawa, Japan, the risk of occurrence of acute myocardial infarction was 2.5 times and 4.6 times higher in male and female hemodialysis patients, respectively, than the general population [4]. Also, the risk of stroke was 5.7 times and 8.5 times higher in male and female hemodialysis patients in their sixties, respectively, than the general population of the same age category [5]. These data do indicate that hemodialysis patients experience more CVD events, but the increased risk of CVD events does not fully explain the 10–30 times higher risk of CVD death. The discrepancy suggests that the risk of death after getting an event (fatality) is also elevated in hemodialysis patients. In fact, the survival curves after acute myocardial infarction are quite different between the hemodialysis and general populations. Death rate in 30 days after acute myocardial infarction was 22.9% for the general population and 50.8% for hemodialysis patients in Okinawa, Japan [4]. The 50% survival period after acute myocardial infarction was 7.3 years for the general population, whereas it was one month for hemodialysis patients. Also, the death rate in 30 days after stroke was 12.3% for the general population and 46.6% for hemodialysis patients in Okinawa, Japan [5]. These data indicate that both the increased incidence of CVD events and increased risk of fatality after CVD events synergistically raise the death risk due to CVD in hemodialysis patients.

Dyslipidemia, atherosclerosis, death from CVD

In the general population, we assume the following two steps from dyslipidemia to CVD death:

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- dyslipidemia promotes atherosclerosis;
- advanced atherosclerosis is associated with increased risk of mortality from CVD.

Therefore, dyslipidemia predicts increased risk of CVD death. In contrast, the same syllogism does not appear to apply to hemodialysis patients. Does this mean that a lower level of cholesterol promotes atherosclerosis? If not, do dialysis patients with advanced atherosclerosis live longer? According to reports from Japan, a higher level of cholesterol excluding high-density-lipoprotein cholesterol (non-HDL-C) was positively associated with morphological and functional changes in arterial wall, measured as carotid artery intima-media thickness (IMT) [6] and aortic pulse wave velocity (PWV) [7]. Also, hemodialysis patients with higher carotid IMT [8] or higher aortic PWV levels [9] were at an increased risk of death from CVD during follow-up. These data show that none of the two is reversed in hemodialysis patients. Then, what makes the reverse epidemiology?

Malnutrition as another player

Malnutrition—inflammation [10] or kidney disease wasting, is an important factor affecting risk of death in hemodialysis patients. A lower BMI is associated with a higher risk of death from all-cause and CVD in hemodialysis patients in France [2], the US [11] and Japan. Recent studies [12,13] showed that a lower fat mass rather than lean mass is an independent

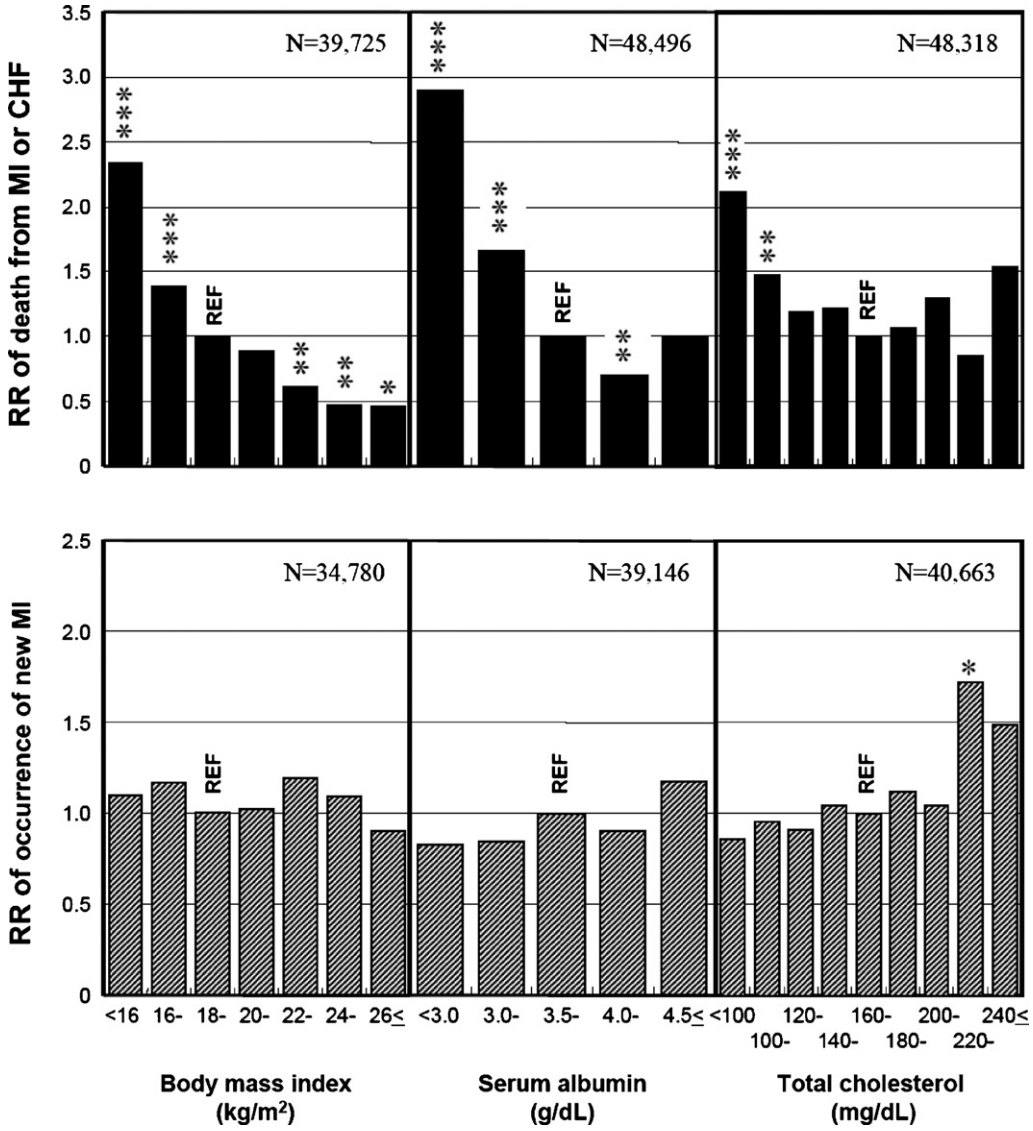

Figure 1 Associations of three nutritional markers with cardiovascular risk using different endpoints among prevalent non-diabetic hemodialysis patients in Japan [15]. Upper panel: BMI, serum albumin and serum total cholesterol levels were inversely associated with one-year risk of death from myocardial infarction or congestive heart failure. Lower panel: One-year risk of new occurrence of myocardial infarction was not significantly associated with body mass index or serum albumin. Total cholesterol showed a positive trend and it reached statistical significance in patients with total cholesterol between 220 and 239 mg/dL. The relative risk was calculated after adjustment for age, sex and duration of dialysis. The figure illustrates the results for non-diabetic hemodialysis patients. Analyses in diabetic dialysis patients gave essentially the same results. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

predictor of all-cause mortality in hemodialysis patients. A lower serum albumin is another predictor of mortality in dialysis populations [14]. Since patients with malnutrition tend to have lower cholesterol levels, one may expect that the cholesterol paradox in hemodialysis patients can be explained by taking malnutrition into account. However, although malnutrition may lower cholesterol levels, lower cholesterol levels are associated with better arterial wall properties even in hemodialysis patients as reviewed above. Therefore, it is reasonable to assume that dyslipidemia and malnutrition affect the risk of death from CVD in different ways.

Does malnutrition really accelerate atherosclerosis?

Does malnutrition increase the risk of CVD event occurrence or risk of death after such an event? There are data to answer this question in the registry data of Japanese Society for dialysis therapy (JSDT). As shown in Fig. 1, the risk of death from cardiac disease (myocardial infarction or congestive heart failure) was inversely associated with BMI and serum albumin levels [15]. However, none of these factors was significantly associated with the risk of new onset of myocardial infarction. These data indirectly suggest that those with low BMI or low albumin levels more likely die after cardiac events than those with high BMI or high albumin levels. Thus, we speculate that malnutrition increases the risk of death by increasing the risk of fatality rather than the risk of event occurrence.

Dyslipidemia increases the risk of cardiac events in hemodialysis

The JSDT registry data, similar to data from other countries, showed that a lower total cholesterol level was associated with a higher risk of death from cardiac disease [15]. Importantly, total cholesterol positively correlated with the risk of incidence of myocardial infarction, although it did not have statistical significance. In Fig. 1, dialysis patients with total cholesterol between 220 and 239 mg/dL had a significantly higher risk of new events of myocardial infarction than those with total cholesterol between 180 and 199 mg/dL. The association between lipid parameters and onset of new myocardial infarction was more impressively demonstrated when dyslipidemia was expressed using low-density-lipoprotein-cholesterol (LDL-cholesterol), HDL-cholesterol and triglycerides (Fig. 2) [16]. It was positively associated with LDL-cholesterol and triglyceride levels and inversely with HDL-cholesterol, similar to data for non-renal populations. These data suggest that dyslipidemia itself is associated with an increased risk for development of myocardial infarction even in the hemodialysis population.

Possible explanation for reverse epidemiology

We previously proposed the following hypothesis [17,18]: Dyslipidemia causes atherosclerotic arterial wall changes that increase the risk of occurrence of CVD events and subsequently increased risk of death from CVD. Malnutrition increases the risk of fatality after CVD events. Since malnourished patients have lower levels of cholesterol, there exists an inverse association between cholesterol and mortality risk. Similar paradoxes can be seen for other risk factors that are affected by nutritional status including homocysteine [19] and advanced glycation end products (AGEs) [20]. Such paradoxical phenomena are seen when the relative importance of fatality risk is substantially elevated over the risk of event occurrence.

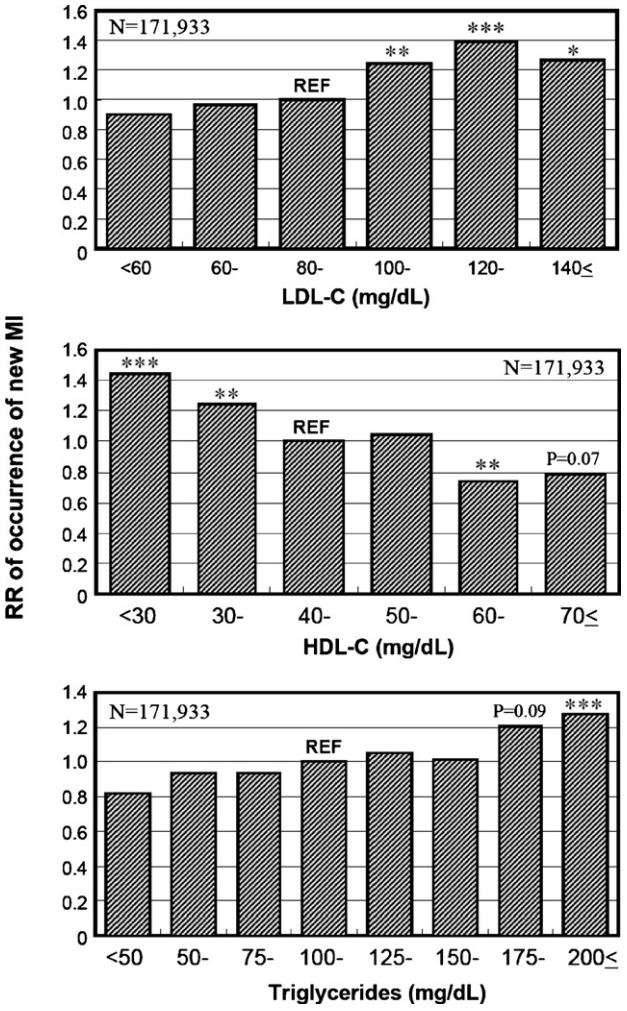

Figure 2 Associations of lipid parameters with risk of new myocardial infarction among prevalent hemodialysis patients in Japan [16].Risk of developing new myocardial infarction in one year was positively associated with LDL-cholesterol and triglycerides and inversely with HDL-cholesterol. The relative risk was calculated after adjustment for age, sex, duration of dialysis and presence of diabetes mellitus. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Examples to test the explanation

If the hypothesis is correct, one may expect that hemodialysis patients without malnutrition have a positive association between cholesterol and mortality risk from all-cause and

CVD. In fact, this is true as shown by an observational cohort study in the US [21]. In addition, non-HDL-C is positively associated with death from CVD in a cohort of Japanese hemodialysis patients [22] who are known to be less inflamed.

If increased fatality risk is important for reverse epidemiology, other populations with high fatality risk are expected to show reverse epidemiology. The risk of fatality is raised not only in dialysis patients but predialysis patients with advanced stages of chronic kidney disease (CKD). As shown in VALIANT [23] that followed patients with acute myocardial infarction, the risk of death from CVD is higher in those with lower estimated GFR (eGFR) levels. Since all subjects had had myocardial infarction at entry, the increased death risk indicates an increased fatality risk. The relative risk of CVD death in patients with eGFR < 45 mL/min/1.73 m^2 was 3.78 as compared to patients with eGFR of 75 or higher. A recent study [24] revealed that the reverse epidemiology is also present in men with advanced CKD not yet on dialysis.

In contrast, the reverse epidemiology is again reversed following successful kidney transplantation [3]. Renal allograft recipients have much better survival curve after acute myocardial infarction than hemodialysis patients [25], suggesting that fatality risk in renal failure patients is significantly decreased with functioning renal allografts.

Conclusions

Most epidemiological studies in dialysis patients reported mortality rather than event occurrence as an endpoint. Although it may cause no major problems in the general population, we now recognize that risk factors for CVD events and death from CVD are not the same as shown by the JSDT. The important point appears to be the significantly increased fatality risk that is closely associated with malnutrition—inflammation in the dialysis population. In our opinion, to reduce the risk of death from CVD in dialysis patients, we should consider risk reduction in both occurrence of CVD events and fatality following such events. Further studies are clearly needed to better understand the biological mechanisms behind the reversed epidemiology and to provide better management for patients with particularly elevated risk of death from CVD.

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