

# Resolved: Being Fat Is Good for Dialysis Patients: The Godzilla Effect

## ABSTRACT

Obesity is the epidemic of the 21st century. Despite the fact that obesity is known to have major health consequences in the general population, an increasing number of large-scale epidemiological studies indicate an inverse association between increasing body mass index and mortality in dialysis patients. Here it is argued pro and con that epidemiological data derived from the healthy general population may or may not be applicable to conditions such as end-stage renal disease.

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## Pro

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Obesity is the epidemic of the 21st century and its health consequences are obvious, including the most important consequence—excess deaths. In spite of the disturbing statistics in the general population, an increasing number of large scale epidemiologic studies indicate an inverse association between increasing body mass index (BMI) and mortality in dialysis patients, a conundrum that has been labeled by some as reverse epidemiology.<sup>1</sup> Even more intriguing are findings indicating that high values for BMI are protective and associated with improved survival on dialysis.<sup>2,3</sup> Given the highly advertised increased burden of chronic disease due to obesity, these data seem counterintuitive and have created debate within the nephrology community.

Several lines of reasoning could explain why the so-called paradoxical epidemiological data in patients with end-stage renal disease (ESRD) is actually logical. First, epidemiological studies examining the burden of disease related to excess weight in healthy individuals should exclude subsets with existing medical conditions.<sup>4</sup> If a relevant public health question is about the optimal BMI that *healthy* individuals should maintain to minimize premature mortality, then those with serious illness at baseline must be eliminated from the analysis.<sup>4</sup> Because dialysis patients by default have a serious illness that alters metabolic pathways, comparison between these groups must be interpreted in that context. Second, most studies that assess BMI in mid-life show that those higher values predict an increased risk of death over subsequent decades. Epidemiological studies that assess BMI only late in life cannot capture potential adverse effects of an elevated mid-life BMI on subse-

quent chronic disease and eventual mortality. Because dialysis events are a disease of the elderly, and even for dialysis patients who are within the age bracket of 45 to 64 (the 10-yr survival probability is only 22%<sup>5</sup>), one would not expect to see the consequences of obesity related to death in such a short period of time. Third, a similar direct association between BMI and survival has been reported in multiple other chronic disease conditions, including congestive heart failure, cancer, HIV, and older age.<sup>6–9</sup> It is only logical to expect the same in dialysis patients. Fourth, data in dialysis patients are obtained from almost 750,000 subjects,<sup>2,3</sup> a robust sample size for drawing inferences. Finally, a simple interpretation of the data associating BMI with survival in dialysis patients is that in the steady state of stable health and adequate or excess dietary nutrient intake, individuals who are able to maintain or gain excess weight are more likely to live longer. Hence, higher BMI in dialysis patients might simply reflect better health status, with BMI merely being a surrogate marker of this phenomenon. Therefore, one can conclude that the positive epidemiological relationship between excess weight and survival advantage in dialysis patients is real and not unexpected. The remaining question is why excess weight is beneficial to dialysis patients.

To answer the question of why obesity is protective in dialysis patients, consideration of both the cause of obesity and the causal pathways through which obesity influences mortality in the set-

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ting of advanced chronic kidney disease are critically important. There is now undisputable evidence to indicate that dialysis patients are subject to multiple metabolic and nutritional derangements leading to a chronic and persistent negative nutrient balance.<sup>10</sup> Anorexia and catabolic effects of dialysis in the setting of inappropriately increased basal energy expenditure lead to a markedly negative energy balance.<sup>11,12</sup> Dialysis patients undergo a worsening of nutrient balance through recurrent acute medical events requiring hospitalizations and a number of other comorbid conditions.<sup>10</sup> These catabolic effects are reflected in well-described loss of weight and subcutaneous adipose tissue over time in hemodialysis patients who survive over a decade.<sup>13</sup> Overall, one can conclude that dialysis patients are in a state of semistarvation that is mediated through multiple mechanisms involving decreased nutrient supply, altered metabolism, and increased nutrient requirements. Regardless of the mechanism, to survive semistarvation, living organisms, especially humans, need adequate energy stores.

Our ability to store energy as fat is essential for life and our capacity to survive starvation is directly dependent on the amount of fat that is stored. This phenomenon has been shown *in vivo*, both in animals experimentally and in humans through observations of unusual occurrences. Increased fat mass in obese rats not only provided extra fuel but also less lean body mass loss compared with lean rats.<sup>14</sup> Cuendet and colleagues also demonstrated that lean mice survived approximately 3 to 7 d during fasting, whereas obese mice survived >4 wk. These experiments highlight the vital importance of adequate fat stores during inadequate macronutrient intake.<sup>15,16</sup>

Obviously, similar studies of prolonged starvation in humans are unethical and are only available as unexpected social experiments. Recent reappraisal of the Minnesota Starvation Experiment, a grueling study meant to gain insight into the physical and psychological effects of semistarvation,<sup>17</sup> indicates that control of partitioning between protein and fat during food shortage is dependent on the baseline fat content and body composition of the specific subject. That is, the basal energy expenditure and physical capability of an individual is directly related to his or her fat stores.<sup>18,19</sup> In relation to the deaths of 10 Irish Republican Army hunger strikers in 1981, fasting survival was dependent on fat more than protein stores.<sup>20</sup> In another group of eight hunger strikers, Faintuch observed the overwhelming participation of body lipids in maintaining energy balance during uncomplicated prolonged starvation,<sup>21</sup> once again highlighting the crucial importance of fat stores during inadequate nutrition.

In addition to its advantage as a source of fuel, adipose tissue can also mediate effects through other mechanisms, directly or indirectly, which may be beneficial in dialysis patients. Adipocytes are critical for health and their absence leads to a state of metabolic dysfunction, including insulin resistance, hyperglycemia, hyperlipidemia, and fatty liver, which can be completely reversed with transplantation of adipose tissue.<sup>22</sup> Adipose tissue also produces more TNF- $\alpha$ -soluble receptors that attenuate the adverse effects TNF- $\alpha$  itself, and obese indi-

viduals have higher lipoprotein concentrations, which counteract the inflammatory effects of circulating endotoxins.<sup>23</sup> Similarly, reductions in total body fat are associated with decreased humoral immunity.<sup>24</sup> Finally, to carry an excess load of fatty tissue, overweight and obese individuals have a higher absolute amount of muscle mass. This increased amount of lean tissue might confer an additional protective edge during times of catabolism.<sup>25</sup>

Despite the intriguing data on the benefits of having excess weight in dialysis patients, there are a number of limitations to consider when interpreting available evidence. First, epidemiological data only generate hypotheses, and the hypothesis of protective or beneficial effects of excess weight in dialysis patients should be tested with appropriately designed prospective randomized trials. There are many disappointing examples in the medical literature where the results of careful, well-designed trials were not in accordance with previous epidemiological data.<sup>26</sup> Second, epidemiological studies do not provide mechanistic information. It is critically important for the readers of this debate to understand why and how excess weight might lead to a survival advantage. Third, most of the epidemiological studies have used BMI as the surrogate marker for excess weight. Not only is BMI a poor anthropometric marker, but it also fails to provide any detailed information about the specific origin of the excess weight, which may have different implications regarding their adverse and potentially beneficial metabolic effects.<sup>27,28</sup> Finally, it is difficult to estimate the burden of disease attributable to obesity, which thwarts assessment of its hazards in complicated patient populations.<sup>29</sup> Therefore, many established risk factors related to excess weight may be less relevant at the time the baseline weight is measured in dialysis patients.

It is important to place the foregoing discussion into a clinical and research context. The most important caveat here is to differentiate between dialysis patients *versus* patients with chronic kidney disease who are not on dialysis. For the latter, the available evidence indicates an adverse effect of excess weight rather than a beneficial effect, including faster progression to ESRD, an increased inflammatory response, more oxidative stress, and worse insulin resistance.<sup>30–32</sup> On the other hand, it is clear that we have to rethink the management of overweight and obese dialysis patients, especially when we make recommendations regarding weight loss. An important implication of obesity in dialysis patients is their suitability for kidney transplantation, which may be affected by BMI. Clinicians are advised to make the most appropriate decision regarding weight loss in dialysis patients that are otherwise suitable for kidney transplantation, especially patients waiting for a living-related donor.

There are also many outstanding research questions that should be answered through appropriately designed prospective studies. To date, there are few randomized trials that evaluate the beneficial effects of nutritional interventions in dialysis patients.<sup>33</sup> The fascinating Janus-like duality of obesity in progressive kidney disease should be the impetus for more

studies. Regardless of the mechanisms involved in this process, the advantages of being overweight or even obese override the associated burden of disease in most dialysis patients.

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## DISCLOSURES

None.

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## Con

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In contrast to the general population, an elevated body mass index (BMI) confers a survival advantage to patients with chronic kidney disease, as first described by Fleischmann *et al.* in 1999.<sup>1</sup> This finding was subsequently confirmed in 54,535 hemodialysis patients showing that even BMI >35 kg/m<sup>2</sup> was associated with a survival advantage.<sup>2</sup> Moreover, a low percentage of body fat, or fat loss over time, was independently associated with higher mortality in 535 hemodialysis patients.<sup>3</sup> However, in a group of 722 European hemodialysis patients, de Mutsert *et al.*<sup>4</sup> found no survival advantage of BMI >30 kg/m<sup>2</sup>. There may be several reasons for these discrepant results.

Obviously, the distribution and prevalence of obesity may be different in the United States compared with Europe. The cause of obesity is multifactorial and includes genetic factors, intrauterine nutrition (epigenetics), and environmental factors such as high-energy intake, more frequent consumption of beverages containing high-fructose corn syrup, low levels of physical activity, drugs, stress, viral infections, and sleep deficits. As the “obesity paradox” is stronger in black dialysis patients, and Asians on hemodialysis in the United States do not have better survival at higher BMI, results obtained in different races or ethnicities may not be readily comparable.<sup>5</sup> Moreover, long-term mortality in the general population has usually been compared with short-term mortality in dialysis patients.<sup>4</sup> This may not be a correct comparison because there are time discrepancies between competing risk factors. Indeed, short term-mortality, as a result of negative nitrogen balance and inflammatory disorders among other causes, is strongly associated with lower BMI in dialysis patients. Of note, there was an equal duration of follow-up between dialysis patients and the general population in the European study.<sup>4</sup> Because the relationship between increased BMI and mortality seems to be less pronounced in the elderly general population, age-related mortality patterns may be another factor contributing to the observed association between elevated BMI and a survival benefit in dialysis patients.

Another major problem when interpreting epidemiological studies is the use of BMI as a surrogate marker for fat mass because BMI does not differentiate between muscle and fat. The fact that BMI is not a reliable marker of fat mass is an important confounder. This is particularly true in dialysis patients where gross imbalances in fluid homeostasis are often observed. Because an increase in BMI may also be caused by

more lean body mass, the association between increased BMI and better outcome does not necessarily imply that fat mass is protective. Indeed, Beddhu *et al.*<sup>6</sup> showed in 70,028 hemodialysis patients (by evaluating 24-h urinary creatinine excretion as a measure of muscle mass) that the protective effect of increased BMI was limited to those with normal or high muscle mass. Although this study has been criticized on methodological grounds, 24-h urinary creatinine excretion is not only related to muscle mass but also renal function and protein intake, so it provides some insight into the association between BMI and outcome. In accordance, a Brazilian study of 344 hemodialysis patients showed that worse survival was found in patients with BMI >25 kg/m<sup>2</sup> and a low muscle mass estimated by mid-arm muscle circumference.<sup>7</sup> A recent study also demonstrated that a higher lean body mass was associated with lower risk of cardiovascular death.<sup>8</sup> Moreover, protein-energy wasting, which also appears to be common (16%) in overweight (BMI > 25 kg/m<sup>2</sup>) stage 5 chronic kidney disease patients, is a predictor of mortality in these patients as well.<sup>9</sup>

Fat tissue is not simply a passive storage depot but the largest endocrine organ in the body, and it secretes a number of pleiotropic adipocytokines such as leptin, adiponectin, resistin, IL-6, and TNF- $\alpha$ .<sup>10</sup> Because increased fat mass is associated with lower adiponectin levels, the recent observation by Menon *et al.*<sup>11</sup> that high rather than low adiponectin levels were associated with increased mortality indirectly suggests that increased fat mass is not associated with a survival advantage in chronic kidney disease. Macrophages resident in adipose tissue are an important source of proinflammatory cytokines and promote oxidative stress and endothelial dysfunction.<sup>10</sup> Because hepatic macrophages (Kupffer cells) make up the largest pool of fixed tissue macrophages and constitute approximately 70% of the total macrophage population in the body, the role of fat accumulation in the liver needs further attention in the context of uremia.

Because increased fat mass is associated with metabolic derangements such as inflammation, insulin resistance, hyperadipokinemia and dyslipidemia, lower quality of life, and sleep apnea, a protective effect of increased fat mass on survival seems counterintuitive. An interesting alternative hypothesis addressing the question of why increased body size may be associated with better outcome was recently presented by Kottanko *et al.*<sup>12</sup> Because generation of uremic toxins occurs predominantly in visceral organs, the generation of toxins per unit of BMI is lower in patients with high BMI who are often subjected to relatively more dialysis, if Kt/V is used to prescribe dose of dialysis. Indeed, because good appetite is associated with better outcome in hemodialysis patients,<sup>13</sup> and obese patients consume more calories, this may indirectly explain the association between high BMI and better outcome.

It should be appreciated that, besides detrimental metabolic effects, increased fat mass may also have, at least in theory, beneficial effects in the uremic milieu. Besides indicating well-preserved energy stores, the presence of obesity may be associated with improved hemodynamic tolerance, better stem cell

mobilization, less stress response as a result of neurohormonal alterations, and more efficient disposal of lipophilic uremic toxins such as p-cresol and pentosidine.

In a study of 808 hemodialysis patients, Kakiya *et al.*<sup>8</sup> demonstrated that higher fat mass was associated with lower risk of noncardiovascular death. However, in this study no differentiation between different areas of fat tissue deposition was made. Because there are significant differences in metabolic activity, gene expression, hormonal sensitivity, and physiology between subcutaneous and visceral fat compartments, the relative importance of various fat stores should be relevant to this argument. Indeed, visceral fat mass is the most metabolically active fat store and a key factor in the development of insulin resistance, type-2 diabetes, and atherosclerosis. Although hemodialysis patients exhibit visceral fat accumulation associated with a disturbed lipid profile, insulin resistance, and carotid atherosclerosis irrespective of BMI,<sup>14</sup> the differential effects of visceral *versus* subcutaneous fat stores on outcome has attracted surprisingly little interest. As preliminary data from Stockholm shows that increased visceral fat mass predicts poor outcome in male but not female dialysis patients, the impact of both gender and the distribution of fat tissue needs further investigation.

On the basis of face-to-face interviews and questionnaires of 926 native Swedes with chronic kidney disease, Ejerblad *et al.*<sup>15</sup> demonstrated that a high BMI was an important risk factor for chronic kidney disease, supporting the concept that obesity should be viewed as major preventable risk factor for renal progression. This is important new information because the majority of chronic kidney disease patients in the United States do not need dialysis.<sup>16</sup> Thus, obese hemodialysis patients may constitute a selected group of survivors with a different genetic framework than their obese counterparts with chronic kidney disease who did not make it to end-stage.

Little is known about genes associated with obesity and their relationship with other genetic traits affecting vascular health. However, emerging data suggest that fetuin-A, a circulating inhibitor of vascular calcification and ossification, is related to both insulin resistance and fat tissue accumulation.<sup>17</sup> Thus, on the basis of a Swedish study showing that a common variant in the fetuin-A gene, which is associated with lower circulating fetuin-A levels, was more common among lean than obese and overweight men,<sup>18</sup> it could be speculated that genetic traits associated with insulin resistance and fat tissue accumulation, rather than obesity *per se*, are associated with survival advantage in chronic kidney disease. Clearly, further studies are needed to see whether genetic traits associated with fat tissue accumulation are associated with survival advantage in chronic kidney disease.

Whereas observational studies show that low BMI is associated with poor outcome in dialysis patients worldwide, epidemiological data relating high BMI to better outcome seems to differ between the United States and Europe. Clearly, cause and consequence can never be detected in cross-sectional studies. In our opinion, statistical fallacies, such as differences in

observation time and age between the general population and dialysis patients, as well as differences in ethnicity and nutritional intake, may contribute to the observed discrepancies. It is also possible that obese patients starting dialysis treatment in the United State may constitute a selected group of survivors that endured the hardship of a longstanding unhealthy uremic milieu. Indeed, because decreased survival was found in 1759 North American patients with chronic kidney disease (GFR  $39 \pm 21$  ml/min) with high BMI, obesity does not seem to be protective in mild to moderate chronic kidney disease.<sup>19</sup>

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## DISCLOSURES

None.

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