University of Groningen

To add weight to overweight

van Gastel, Maatje D.A.; Meijer, Esther

Published in:
Clinical Journal of the American Society of Nephrology

DOI:
[10.2215/CJN.04150321](https://doi.org/10.2215/CJN.04150321)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):
van Gastel, M. D. A., & Meijer, E. (2021). To add weight to overweight. *Clinical Journal of the American Society of Nephrology*, 16(6), 850-852. <https://doi.org/10.2215/CJN.04150321>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

To Add Weight to Overweight

Maatje D.A. van Gastel and Esther Meijer

CJASN 16: 850–852, 2021. doi: <https://doi.org/10.2215/CJN.04150321>

In autosomal dominant polycystic kidney disease (ADPKD), cyst formation leads to kidney failure, at a mean age of 58 years. Because of its inherently progressive nature, ADPKD accounts for 10% of all patients receiving kidney function replacement therapy. So far, there is only one treatment proven to be beneficial in ADPKD. This drug, a vasopressin V2 receptor antagonist (1), is expensive, and because of its aquatic adverse events, it is not tolerated by all patients. As ADPKD is an inherited disease, patients see their parents in dialysis or after kidney transplantation and are very motivated to undergo treatment in order to delay or preferably prevent necessity of KRT. One of the most frequently asked questions at the outpatient clinic is what a patient can do his- or herself to postpone kidney failure.

The relative lack of treatment, inevitability of kidney failure, and high motivation of patients emphasize the importance of investigating lifestyle as treatment in ADPKD. Because vasopressin has a central role in the pathophysiology, it makes sense to investigate lifestyle habits that influence vasopressin, such as decreasing salt and increasing water intake. Also in obesity, vasopressin levels are elevated (2). Another reason to study obesity in ADPKD is the mounting evidence that metabolic defects are a key feature of ADPKD. In ADPKD, the glucose metabolism is altered (3), and food restriction has been shown to be beneficial in animal models (4). In a previous *post hoc* analysis of the Halt Progression of Polycystic Kidney Disease (HALT-PKD) studies, overweight and obesity were found to be predictors of disease progression in ADPKD (5).

As proxy for adiposity and overweight, body mass index (BMI) is frequently used because it is easy to measure and calculate. It was developed by Adolphe Quetelet during the nineteenth century, and it is the most commonly used tool to correlate weight with risk of health problems at the population level. BMI is associated in the general population with premature death, cardiovascular diseases, high BP, osteoarthritis, some cancers, and diabetes. It is also associated with new onset of kidney disease and reaching ESKD (6).

In this issue of *CJASN*, Nowak et al. (7) investigate the association between BMI and disease progression in patients with ADPKD. In total, 1312 patients with ADPKD who participated in the Tolvaptan Phase 3 Efficacy and Safety Study in Autosomal Dominant

Polycystic Kidney Disease (TEMPO 3:4) (1) were categorized as having normal weight, overweight, or obesity. BMI was also investigated as a continuous variable. The TEMPO 3:4 study is the landmark study of vasopressin V2 receptor antagonism in ADPKD. This study included patients with early ADPKD who had a high likelihood of rapid disease progression. The authors found that in fully adjusted models, higher BMI was associated with greater annual increase in percentage total kidney volume (TKV). For every 5 units higher BMI, annual TKV increased 1%. Annual eGFR decline, however, did not differ according to BMI. Furthermore, BMI did not affect the treatment efficacy of tolvaptan.

Why did the authors find an association with BMI and increase in TKV but not with change in eGFR? Several explanations come to mind.

First of all, it could be that the association is present but that it is not found because of the population under study. In the HALT-PKD study, the same research group did find an association between BMI and kidney function decline (5). This association was, however, not very strong (fully adjusted $\beta = -0.08$; 95% confidence interval, -0.15 to -0.02). Compared with this study, obesity was slightly less prevalent (16% versus 18%), eGFR decline was slightly less (-2.55 versus -3.2 ml/min per 1.73 m² per year), and the follow-up was shorter (3 versus 8 years). This study is, on the other hand, larger (1312 versus 441 patients). In both studies, patients with ADPKD were in an early disease stage (eGFR with the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula of 78 ± 22 in this study versus eGFR of 90 in the previous study). Not finding an association in this study might be due to the relatively short follow-up time (36 months). Second, it could be a methodological issue. For TKV, an adjusted BMI was calculated to remove the contribution of the kidneys to overall body weight, and a percentage increase is chosen to adjust for a larger baseline kidney volume (because larger kidneys will probably grow larger absolute volumes). It is of interest that the authors did not use height-adjusted TKV in these analyses. As BMI itself is dependent on height and weight, it makes sense to not correct your outcome variable for either of these two. For kidney function estimation, however, the authors used the CKD-EPI formula, which corrects for body surface area. This might reduce the chance of finding an

Division of Nephrology,
Department of Internal
Medicine, University
Medical Center
Groningen, University
of Groningen,
Groningen, The
Netherlands

Correspondence:

Dr. Esther Meijer,
Division of
Nephrology,
Department of
Medicine, University
Medical Center
Groningen,
PO Box 30.001, 9700
RB Groningen,
The Netherlands.
Email: esther.meijer@umcg.nl

association. As patients with a higher BMI have a larger body surface area, they will have a higher kidney function at baseline and perhaps, a greater change in kidney function over time when not adjusting for body surface area. Also, although the CKD-EPI formula performs relatively well, it remains an estimate. It is, therefore, of interest to re-evaluate these analyses with measured GFR instead of eGFR. Finally, it could also be that there is an association between adiposity and kidney function, but BMI is not an appropriate measure. BMI is only dependent on height and weight, and it does not take into consideration different levels of adiposity on the basis of age, physical activity levels, and sex. Although analyses are corrected for age and sex, it can be expected that BMI overestimates adiposity in some cases and underestimates it in others. This underestimation is especially the case in CKD, where sarcopenia (reduction of muscle mass) is prevalent (8).

Another explanation could be that BMI is associated with TKV but truly not with kidney function. Perhaps the association between TKV and kidney function in ADPKD is not as straightforward as we think. It is very likely that kidney function decline is dependent on more factors than cyst growth only because there are numerous patients with ADPKD and relatively preserved kidney function despite a large TKV and the other way around. These differences in trajectories of kidney growth and kidney function decline are also observed in intervention studies in ADPKD. For instance, the vasopressin receptor antagonist extension study, TEMPO 4:4, did not demonstrate a sustained expected beneficial difference in TKV achieved during the primary trial, but it did show a sustained beneficial effect on eGFR (9). The opposite happens in the Developing Intervention strategies to halt Progression of Autosomal Dominant Polycystic Kidney Disease-1 (DIPAK-1) trial, where lanreotide decreases kidney volume but does not have an effect on kidney function (10). In this case, BMI could have an effect on TKV but not, or less so, on kidney function.

As the authors state, it is not known whether the found association is causal. Smoking and physical activity could be potential confounders that were not collected in the study. BMI is known to be part of the metabolic syndrome, together with glucose intolerance, dyslipidemia, and hypertension. In this study from Nowak *et al.* (7), patients with a higher BMI also have higher BP and fasting glucose levels, suggesting that not only BMI but the whole metabolic syndrome could be associated with TKV in these patients.

Then, if TKV or the whole metabolic syndrome is associated with disease progression, what could be the underlying mechanism? In the general population, studies have demonstrated that overweight leads to kidney hyperperfusion and glomerular hyperfiltration. Because albuminuria, a key feature in hyperfiltration, is not higher in obese patients with ADPKD in this study, this mechanism seems less likely. An alternative hypothesis could be the vasopressin pathway because vasopressin is increased in patients with metabolic syndrome (2) and known to cause disease progression in ADPKD. However, in this study, addition of copeptin to the multivariable models did not affect the association between BMI and kidney growth, suggesting that copeptin is not a major mediating factor either. The most likely explanation is that overnutrition and obesity activate pathways that induce cyst growth. Preclinical studies show

evidence for activation of mechanistic target of rapamycin, amongst others, as described in a review by some of the same authors recently (11).

Strengths of this study are the clinical relevance of this subject. The manuscript is very clearly written, with insightful statistics. The study includes a large number of patients, and we appreciate the inclusion of copeptin as a potential mediator in these analyses.

Limitations of this study are the associative nature of the *post hoc* analysis. BMI might not be the best measure for adiposity in patients with kidney function decline and should perhaps be seen as part of the metabolic syndrome. The lack of finding an association with kidney function decline decreases the clinical importance, as patients with ADPKD ultimately should be directed toward treatment that slows kidney function decline rather than treatment that only affects kidney growth.

In conclusion, maintaining a healthy weight is important. We already knew that overweight and obesity were associated with premature death, cardiovascular diseases, high BP, osteoarthritis, some cancers, and diabetes. Now, we can add that in ADPKD, overweight and obesity are associated with more rapid kidney growth. This promising study raises additional questions. Is it BMI only or is the whole metabolic syndrome associated with disease progression? Is there only an association with TKV or also with kidney function decline? We are eager to learn what causes the found association and if lowering BMI leads to kidney function protection in prospective studies.

Disclosures

E. Meijer reports employment with University Medical Center Groningen, Groningen, The Netherlands; receiving research funding from Ipsen, Otsuka Pharmaceuticals, and Sanofi, with all money paid directly to the institution; and other interests/relationships with the Dutch Kidney Foundation, Health Holland, Nieren.nl, NvN, and werkgroep erfelijke nierziekten. M.D.A. van Gastel reports employment with University Medical Center Groningen.

Funding

None.

Acknowledgments

The authors thank Prof. RT Gansevoort for critical reading and suggestions to our editorial. The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or CJASN. Responsibility for the information and views expressed herein lies entirely with the author(s).

References

1. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Grantham JJ, Higashihara E, Perrone RD, Krasa HB, Ouyang J, Czerwiec FS; TEMPO 3:4 Trial Investigators: Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 367: 2407–2418, 2012
2. Enhörning S, Struck J, Wirfält E, Hedblad B, Morgenthaler NG, Melander O: Plasma copeptin, a unifying factor behind the metabolic syndrome. *J Clin Endocrinol Metab* 96: E1065–E1072, 2011
3. Rowe I, Chiaravalli M, Mannella V, Ullisse V, Quilici G, Pema M, Song XW, Xu H, Mari S, Qian F, Pei Y, Musco G, Boletta

- A: Defective glucose metabolism in polycystic kidney disease identifies a new therapeutic strategy. *Nat Med* 19: 488–493, 2013
4. Warner G, Hein KZ, Nin V, Edwards M, Chini CC, Hopp K, Harris PC, Torres VE, Chini EN: Food restriction ameliorates the development of polycystic kidney disease. *J Am Soc Nephrol* 27: 1437–1447, 2016
 5. Nowak KL, You Z, Gitomer B, Brosnahan G, Torres VE, Chapman AB, Perrone RD, Steinman TI, Abebe KZ, Rahbari-Oskouei FF, Yu ASL, Harris PC, Bae KT, Hogan M, Miskulin D, Chonchol M: Overweight and obesity are predictors of progression in early autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 29: 571–578, 2018
 6. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS: Body mass index and risk for end-stage renal disease. *Ann Intern Med* 144: 21–28, 2006
 7. Nowak KL, Steele C, Gitomer B, Wang W, Ouyang J, Chonchol MB: Overweight and obesity and progression of ADPKD. *Clin J Am Soc Nephrol* 16: 908–915, 2021
 8. Sharma D, Hawkins M, Abramowitz MK: Association of sarcopenia with eGFR and misclassification of obesity in adults with CKD in the United States. *Clin J Am Soc Nephrol* 9: 2079–2088, 2014
 9. Torres VE, Chapman AB, Devuyst O, Gansevoort RT, Perrone RD, Dandurand A, Ouyang J, Czerwiec FS, Blais JD; TEMPO 4:4 Trial Investigators: Multicenter, open-label, extension trial to evaluate the long-term efficacy and safety of early versus delayed treatment with tolvaptan in autosomal dominant polycystic kidney disease: The TEMPO 4:4 Trial. *Nephrol Dial Transplant* 33: 477–489, 2018
 10. Meijer E, Visser FW, van Aerts RMM, Blijdorp CJ, Casteleijn NF, D'Agnolo HMA, Dekker SEI, Drenth JPH, de Fijter JW, van Gastel MDA, Gevers TJ, Lantinga MA, Losekoot M, Messchendorp AL, Neijenhuis MK, Pena MJ, Peters DJM, Salih M, Soonawala D, Spithoven EM, Wetzels JF, Zietse R, Gansevoort RT; DIPAK-1 Investigators: Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease: The DIPAK 1 randomized clinical trial. *JAMA* 320: 2010–2019, 2018
 11. Nowak KL, Hopp K: Metabolic reprogramming in autosomal dominant polycystic kidney disease: Evidence and therapeutic potential. *Clin J Am Soc Nephrol* 15: 577–584, 2020

Published online ahead of print. Publication date available at www.cjasn.org.

See related article, “Overweight and Obesity and Progression of ADPKD,” on pages 908–915.