Bariatric surgery helps to reduce blood pressure - insights from GATEWAY trial

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While there is much observational evidence that weight loss and bariatric surgery lead to a sustained reduction in blood pressure,1,2 until the Gastric Bypass to Treat Obese Patients With Steady Hypertension (GATEWAY) trial, there has been no randomized bariatric surgery study in hypertensive subjects where hypertension remission and/or reduction of antihypertensive medications were used as primary outcomes.3 The GATEWAY trial prospectively randomized 100 obese individuals with established but controlled hypertension to either Roux-en-Y gastric bypass (RYGB) or conventional medical therapy. At the 12-month follow-up >80% of the subjects in the surgery group had been able to stop or reduce their antihypertensive medication compared with only ~13% in the medication group. This conclusively shows that RYGB surgery is an effective treatment of hypertension.

While GATEWAY is a well-designed study, a few caveats limit the generalizability of the results. It will be of great interest to see what the planned 5-year follow-up data will show given that hypertension has been shown to relapse in >20% of the subjects within the first 3 years after bariatric surgery.4 Furthermore, GATEWAY did not include individuals with extreme forms of obesity (BMI ≥ 40 kg/m²), current smokers and the majority were females (~70%). Ethnic considerations are also important as the majority were white and it is possible that race impacts on hypertension and sensitivity to different drugs and/or surgery.5

In any case, with the results from GATEWAY as well as previous studies, the scientific community can now shift its focus to understanding how bariatric surgery improves blood pressure. Given the multifactorial causes of hypertension, the beneficial effects are most probably dependent on several different mechanisms. As discussed,6 these may include increased physical activity, reduced sleep apnea, changes in diet (and microbiota?), altered activity in the sympathetic nervous system and improved insulin sensitivity.

The most dramatic change following bariatric surgery is in white adipose tissue (WAT) mass and phenotype. It has therefore been proposed that WAT may play a causal role in explaining the improvements in blood pressure. WAT expresses and secretes a large number of polypeptides (collectively termed adipokines) and non-peptide factors, which may exert both local and systemic effects. Obese WAT is characterized by chronic low-grade inflammation, fibrosis, oxidative stress and an altered balance between vasoconstrictors/dilators (e.g. endothelin and nitric oxide), all of which may impact on vascular phenotype and thereby...
increase blood pressure. In addition, effects on the microcirculation may impair peripheral organ perfusion that could contribute to end-organ damage. While not completely understood, changes in WAT phenotype are regulated by transcriptional and epigenetic mechanisms. The former could be influenced by microRNAs which silence gene expression and thereby affect WAT and/or endothelial function.

Obesity is also characterized by greater overall blood volume, which may depend on both an increased lean body mass and an activation of the renin-angiotension-aldosterone system (RAAS). RAAS activation may in turn be caused by an overactive sympathetic nervous system, mechanical compression of the kidneys by WAT and also by the WAT-dependent secretion of peptides such as angiotensinogen. The ensuing aldosterone release leads to activation of the mineralocorticoid receptor (MR) both in the kidney and also in extra-renal tissues such as WAT. While MR activation plays a role in normal adipocyte differentiation and adipogenesis, the supra-normal levels in obese WAT have been linked to an increase in oxidative stress, dysregulation of adipose autophagy and production of pro-inflammatory adipokines.

Moreover, elevated circulating free fatty acid (FFA) levels, which are increased in obesity, have also been reported to constitute a risk factor for hypertension.

Obesity is characterized by arterial stiffness, an important factor underlying the development of hypertension. As discussed elsewhere, cross-sectional studies have shown that arterial stiffness correlates with adipokine secretion, inflammation and plasma FFA levels. This has prompted several investigators to determine the effects of weight loss on different measures of arterial stiffness. A meta-analysis of 20 studies showed that weight loss leads to a significant reduction in arterial stiffness and blood pressure. However, the causal mechanisms and the contribution of WAT remain unclear. We recently studied which morphologic and functional WAT parameters including gene expression that correlated best with improved arterial stiffness 2 years after bariatric surgery. After correction for multiple confounders, this showed that subcutaneous fat cell volume and WAT expression of a collagen-encoding gene (COL4A1) were independent predictors. While this was a prospective observational study (which excluded subjects on antihypertensive therapies), it nevertheless suggests that WAT-related factors may play pathophysiologic role in explaining the changes in arterial stiffness and thereby blood pressure following weight loss. However, it still does not provide a causal link between WAT and arterial stiffness/blood pressure.

It is important to stress that most studies of WAT have focused on subcutaneous abdominal WAT; for obvious ethical and practical reasons, the role of visceral WAT depots has been less well-characterized. Also of particular interest is the perivascular WAT (pWAT) that surrounds all major arteries and could therefore have a direct paracrine and/or vaso- crine effect on vessel function. pWAT affects vascular homeostasis through both contractile/dilating and pro-/anti-inflammatory factors and this balance is altered in obesity. It is also possible that the arteries affect pWAT function thereby creating a vicious circle. Recent advances in imaging infrared pWAT in man may help us to better understand these mechanisms.

At the moment, it is difficult to determine the relative contribution of WAT on blood pressure improvements following weight loss. In the GATEWAY trial, similar to many other prospective studies, the reduction in blood pressure was observed rapidly, already after 1 month and plateaued at 6 months post-surgery. As body weight reduction (and thereby WAT mass loss) is gradual and reaches a maximum after 1–2 years, it is unlikely that WAT contributes to a major extent in the initial phase of blood pressure improvement. In addition, while bariatric surgery leads to both short- (1 month) and long-term (6–12 months) improvements in systemic inflammation (determined by plasma C-reactive protein levels), the pro-inflammatory phenotype in subcutaneous WAT remains for considerably longer time. Altogether, these observations suggest that subcutaneous WAT cannot explain the rapid improvements in blood pressure following bariatric surgery but may be more important in conferring long-term remission of hypertension. Notably, the incretin effect, which is important for the rapid diabetes remission following bariatric surgery, has only a minor (at best) influence on blood pressure.

A number of outstanding questions remain where the contribution of both clinical and basic scientists is needed. In the GATEWAY trial, ~25% of the subjects in the surgery group remained on two or more antihypertensive drugs suggesting the need for better selection criteria, particularly given the non-negligible morbidity associated with bariatric surgery. Given the world-wide obesity epidemic and the concomitant increase in metabolic complications including hypertension, surgery can never constitute a first-line treatment. Instead, teasing out the mechanisms linking obesity to hypertension is crucial in developing new drugs. Recent studies in obese animal models have tried to identify the causal links between obesity, arterial stiffness and blood pressure. These have focused on pWAT phenotype and the interaction between immune cells and endothelial dysfunction. It would be of great interest to see experimental studies focusing on WAT-specific mechanisms linked to vascular function. Here, several questions need to be answered; are there different mechanisms behind improvements in blood pressure when undergoing bariatric surgery compared to other means of weight loss? Which pathways confer the immediate improvements in blood pressure compared to later? How much is explained by changes in diet and physical activity vs altered WAT phenotype? Do different WAT depots respond differently to bariatric surgery? What are the key changes in the WAT transcriptome/secretome driving these changes? While it is difficult to envision interventions affecting WAT depots selectively, therapies that alter pWAT phenotype (inflammation, secretion?) are of potential interest but need to be studied in animals first, keeping in mind the advantages and limitations of these models.

Finally, will GATEWAY impact on clinical routines? At the moment, this seems less likely, in part due to the limitations of the trial discussed earlier. Furthermore, hypertension is rarely the sole metabolic complication of obesity and it is most often controllable with inexpensive and well-established medications. Nevertheless, the trial gives clinicians further support in recommending RYGB for a subset of obese subjects displaying important cardiovascular risk factors including hypertension.

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References