Positive Relationship Between Plasma Leptin Levels and Hypertension From an Epidemiological Perspective

Jørgen Jeppesen, Camilla Asferg

It is well-documented that a higher body mass index (BMI) is associated with a greater risk of hypertension, even among those with a BMI within the “normal” range.\(^1\) \(^2\) Also, from the field of population sciences, it has been shown that it is a higher BMI caused by fat accumulation, and not by muscle growth, that is the problem. Thus, in a prospective study of >3000 subjects, it was a higher fat mass, and not a higher fat-free mass, that was associated with a greater risk of hypertension.\(^2\)

So, how does fat tissue lead to hypertension? In this context, there has been a change in the way we look at the functions of fat tissue. The traditional view of fat tissue as a passive reservoir for energy storage is no longer valid.\(^3\) On the contrary, fat tissue is an active metabolic and endocrine organ that secretes hormones and cytokines with vascular and inflammatory effects.\(^3\) These hormones and cytokines are described as adipocytokines, and because of the close relationship between overweight and various diseases, these adipocytokines are regarded as possible intermediaries between fat tissue and adiposity-related diseases, including hypertension.\(^4\)

Leptin is one such adipocytokine.\(^3\) Leptin is primarily secreted by fat cells in proportion to fat cell mass. Thus, in a human study, the correlation coefficient for the association between serum leptin levels and percentage of body fat was found to be as high as 0.85, a figure that was higher than the correlation coefficient found for the association between leptin levels and BMI (\(r=0.66\)).\(^4\) So, no matter what functions leptin may have, the level of leptin will generally always be a good biomarker for the amount of body fat, which, as described above, is an important determinant of hypertension risk. In this context, it is important to remember that simply because of leptin’s close association with the amount of body fat, leptin levels will always also be relatively closely associated with all of the other factors that are closely associated with the amount of body fat and regarded as possible intermediaries between fat tissue and development of hypertension, such as higher glucose and insulin levels, and higher levels of inflammatory markers, for example, interleukin 6 and C-reactive protein. Leptin is, at the moment, a relatively strong candidate intermediary between fat tissue and development of hypertension, primarily based on experimental animal studies,\(^4\) although several human studies also support leptin’s candidacy as a mediator in adiposity-related hypertension.

In this issue of *Hypertension*,\(^6\) Shankar and Xiao present interesting cross-sectional data from the Third National Health and Nutrition Examination Survey, which provide further support for leptin’s candidacy as a useful biomarker of hypertension risk and as an intermediary between fat tissue and the development of hypertension. However, before we described their contributions in detail, it is appropriate to review some of the existing data with respect to leptin and hypertension from an epidemiological perspective.

In the field of epidemiology, prospective cohort studies are considered to have greater scientific value than cross-sectional studies, because the prospective study design makes it possible to document that the alleged cause or marker of a disease was present before the development of the disease. So far, 4 studies have been published where the relationship between circulating leptin levels and the development of hypertension has been investigated; 3 studies reported a positive relationship, but 1 found no relationship. The first prospective study by Galletti et al\(^7\) included 489 normotensive men, mean age 50±7 years, with a relatively high prevalence of overweight and obesity. Galletti et al\(^7\) showed in 3 different models that higher leptin levels at baseline were associated with an increased risk of new-onset hypertension independent of baseline age, BMI, systolic blood pressure (BP), and estimates of insulin resistance.\(^7\) Asferg et al\(^8\) studied 920 normotensive women and normotensive men, mean age 45±9 years, with a relatively low prevalence of overweight and obesity. Asferg et al\(^8\) showed that higher leptin levels at baseline predicted new-onset hypertension in models adjusted for baseline and included the following: (1) age, sex, estimated glomerular filtration rate (eGFR), adiponectin, lipids, fibrinogen, and glucose; (2) age, sex, eGFR, adiponectin, and heart rate; (3) age, sex, eGFR, adiponectin, smoking, physical activity, and alcohol consumption; (4) age, sex, eGFR, and BMI or waist circumference or waist:hip ratio; and (5) age, sex, eGFR, and systolic and diastolic BPs.\(^8\)

Published online in 2010, Kramer et al\(^9\) investigated 602 normotensive women and men, mean age 66±11 years, with a relatively low prevalence of overweight and obesity. They found that baseline leptin levels predicted incident hypertension after adjustment for baseline age, BMI, systolic BP, cholesterol, medication, and other cardiovascular diseases.\(^9\) They also reported that further adjustments for estimates of insulin resistance, triglycerides, and waist circumference or waist:hip ratio, in stead of BMI, did not change the results.\(^9\) However, one prospective study, including 748 middle-aged normotensive women and men from the Medical Research

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Council Ely Study, did not find that leptin was significantly associated with incident hypertension. In that study, all of the outcomes were adjusted for baseline BMI. At this point, from an epidemiological perspective, it is relevant to discuss the appropriateness of adjustments for BMI or other measures of overweight when studying possible intermediate variables in overweight-related diseases. It should be remembered that an intermediate variable is a factor that represents a step in the causal chain between the exposure (eg, overweight) and the disease (hypertension). In contrast, a confounder is a variable that correlates with both the exposure and the outcome but is not a step in the causal chain between the exposure and the outcome. Accordingly, adjustments for BMI or other measures of overweight may be considered inappropriate (overadjustment) when studying possible mediators of overweight-related hypertension (eg, leptin), because these factors are intermediate steps between overweight and hypertension.

So, after this summary and theoretical epidemiological consideration, it is time to return to the study by Shankar and Xiao. The study is remarkable for its size, for its inclusion of a large multiethnic representative sample of US adults, and for its inclusion of a great number of possible intermediaries and confounders relevant to overweight-related hypertension in their analyses. However, it is a limitation that they do not in detail discuss the concept of an intermediate variable versus a confounding variable with respect to the way they constructed their logistic regression models, and, in our view, their principal logistic regression models do not include all of the important variables. The most important variables are first introduced in their supplementary analyses. Specifically, Shankar and Xiao do not discuss the possibility of an overadjustment with respect to BMI, as they do not discuss the possibility that leptin may indeed be a better marker of hypertension risk than BMI, as leptin levels may better reflect the amount of body fat, the real underlying problem, compared with BMI. Therefore, the results of their principal analyses are basically confirmatory to what was already reported in the prospective studies, showing again that higher leptin levels are related to higher risk of hypertension and higher BP. In addition, instead of performing stratified analyses by sex and BMI, interaction analysis would probably have been better, because this analytic approach adjusts for uneven distribution of variables among women and men and normal weight and overweight subjects. Nevertheless, the real interesting findings of the study are reported in the supplementary analyses. Here Shankar and Xiao make additional adjustments for serum triglycerides, fasting insulin, C-reactive protein, and resting heart rate (estimate of sympathetic nervous system activity), all variables proposed to be involved in the pathogenesis of overweight-related hypertension. The results show that leptin, insulin, and C-reactive protein were all significantly related to hypertension. These findings support the notion that many different pathways may mediate the BP raising of fat tissue. In addition, as correctly acknowledged by Shankar and Xiao, their study has more limitations, because no measurements were made of other possible important mediators of adiposity-related hypertension, such as adiponectin and components of the renin-angiotensin-aldosterone system. In addition, no data on salt intake or physical activity were reported.

Finally, as this commentary looks at leptin and hypertension from an epidemiological perspective, another advance in the field of epidemiology should be mentioned. Classic epidemiology can only describe associations, and intervention studies directed toward the exposure are needed to document the true cause-and-effect relationship. A new approach to investigate whether a factor is causally related to a variable is mendelian randomization. Mendelian randomization takes advantage of the random assortment of genes that occurs during gamete formation and provides a relatively unbiased method of assessing whether a risk factor, which has a genetic component, is causally related to a variable. Thus, in this case, genotypes, which specifically increase plasma leptin levels, provide a perfect model to assess whether lifelong higher plasma leptin levels influence BP levels, independent of other risk factors. So, if genetic material is available from the Third National Health and Nutrition Examination Survey population, use of mendelian randomization may be a constructive way to obtain further epidemiological support for leptin’s candidacy as an intermediary between fat tissue and development of hypertension.

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