Hypertension and Obesity and the Risk of Kidney Cancer in 2 Large Cohorts of US Men and Women

Abstract
Kidney cancer incidence is increasing globally. Reasons for this rise are unclear but could relate to obesity and hypertension. We analyzed longitudinal relationships between hypertension and obesity and kidney cancer incidence in 156,774 participants of the Women’s Health Initiative clinical trials and observational studies >10.8 years. In addition, we examined the effect of blood pressure (BP) on kidney cancer deaths for >25 years among the 353,340 men screened for the Multiple Risk Factor Intervention Trial (MRFIT). In the Women’s Health Initiative, systolic BP (SBP) was categorized into 6 groups from <120 to >160 mmHg, and body mass index was categorized using standard criteria. In age-adjusted analyses, kidney cancer risk increased across SBP categories (P value for trend <0.0001) and body mass index categories (P value for trend <0.0001). In adjusted Cox proportional hazards models, both SBP levels and body mass index were predictors of kidney cancer. In the MRFIT sample, there were 906 deaths after an average of 25 years of follow-up attributed to kidney cancer among the 353,340 participants aged 35 to 57 years at screening. The risk of death from kidney cancer increased in a dose–response fashion with increasing SBP (hazard ratio, 1.87 for SBP>160 versus <120 mmHg; 95% confidence interval, 1.38–2.53). Risk was increased among cigarette smokers. Additional research is needed to determine the pathophysiologic basis of relationships between both higher BP and the risk of kidney cancer, and whether specific drug therapies for hypertension can reduce kidney cancer risk.
Abstract

Obesity increases preeclampsia risk, and maternal dyslipidemia may result from exaggerated adipocyte lipolysis. We compared adipocyte function in preeclampsia with healthy pregnancy to establish whether there is an increased lipolysis. Subcutaneous and visceral adipose tissue biopsies were collected at cesarean section from healthy (n=31) and preeclampsia (n=13) mothers. Lipolysis in response to isoproterenol (200 nmol/L) and insulin (10 nmol/L) was assessed. In healthy pregnancy, subcutaneous adipocytes had higher diameter than visceral adipocytes (P<0.001). Subcutaneous and visceral adipocyte mean diameter in preeclampsia was similar to that in healthy pregnant controls, but cell distribution was shifted toward smaller cell diameter in preeclampsia. Total lipolysis rates under all conditions were lower in healthy visceral than in subcutaneous adipocytes but did not differ after normalization for cell diameter. Visceral adipocyte insulin sensitivity was lower than subcutaneous in healthy pregnancy and inversely correlated with plasma triglyceride (r=-0.50; P=0.004). Visceral adipose tissue had lower adrenocorticotropin beta 3, lipoprotein lipase, and leptin and higher insulin receptor messenger RNA expression than subcutaneous adipose tissue. There was no difference in subcutaneous adipocyte lipolysis rates between preeclampsia and healthy controls, but subcutaneous adipocytes had lower sensitivity to insulin in preeclampsia, independent of cell diameter (P<0.05). In preeclampsia, visceral adipose tissue had higher lipoprotein lipase messenger RNA expression than subcutaneous. In conclusion, in healthy pregnancy, the larger total mass of subcutaneous adipose tissue may release more fatty acids into the circulation than visceral adipose tissue. Reduced insulin suppression of subcutaneous adipocyte lipolysis may increase the burden of plasma fatty acids that the mother has to process in preeclampsia.
Abstract
Maternal prepregnancy obesity is associated with impaired cardiometabolic health in offspring. Whether these associations reflect direct intrauterine causal mechanisms remains unclear. In a population-based prospective cohort study among 4871 mothers, fathers, and their children, we examined the associations of both maternal and paternal prepregnancy body mass index (BMI) with childhood body fat distribution and cardiometabolic outcomes and explored whether any association was explained by pregnancy, birth, and childhood factors. We measured childhood BMI, total body and abdominal fat distribution, blood pressure, and blood levels of lipids, insulin, and C-peptide at the age of 6 years. We observed that higher maternal and paternal prepregnancy BMI were associated with higher childhood BMI, total body and abdominal fat mass measures, systolic blood pressure, and insulin levels and lower high-density lipoprotein cholesterol levels (P < 0.05). Stronger associations were present for maternal than for paternal BMI, with statistical support for heterogeneity between these associations. The associations for childhood fat mass and cardiometabolic outcomes attenuated after adjustment for childhood current BMI. Compared with children from normal-weight mothers, those from obese mothers had increased risks of childhood overweight (odds ratio, 3.84 [95% confidence interval, 3.01–4.90]) and clustering of cardiometabolic risk factors (odds ratio, 3.00 [95% confidence interval, 2.09–4.34]).

Smaller effect estimates for these outcomes were observed for paternal obesity. In conclusion, higher maternal and paternal prepregnancy BMI were associated with an adverse cardiometabolic profile in offspring, with stronger associations present for maternal prepregnancy BMI. These findings suggest that maternal prepregnancy BMI may influence the cardiometabolic health of offspring through direct intrauterine mechanisms.
CYP2J2 Targeting to Endothelial Cells Attenuates Adiposity and Vascular Dysfunction in Mice Fed a High-Fat Diet by Reprogramming Adipocyte Phenotype

Abstract

Obesity is a global epidemic and a common risk factor for endothelial dysfunction and the subsequent development of diabetes mellitus and vascular diseases, such as hypertension. Epoxyeicosatrienoic acids (EETs) are cytochrome P450 (CYP)-derived metabolites of arachidonic acid that contribute to vascular protection by stimulating vasodilation and inhibiting inflammation. Heme oxygenase-1 is a stress response protein that plays an important cytoprotective role against oxidative insult in diabetes mellitus and cardiovascular disease. We recently demonstrated interplay between EETs and heme oxygenase-1 in the attenuation of adipogenesis. We examined whether adipocyte dysfunction in mice fed a high-fat diet could be prevented by endothelial-specific targeting of the human CYP epoxygenase, CYP2J2. Tie2-CYP2J2 transgenic mice, fed a high-fat diet, had a reduction in body weight gain, blood glucose, insulin levels, and inflammatory markers. Tie2-CYP2J2 gene targeting restored HF-mediated decreases in vascular heme oxygenase-1, Cyp2C44, soluble epoxide hydrolase, phosphorylated endothelial nitric oxide synthase, phosphorylated protein kinase B, and phosphorylated adenosine monophosphate protein kinase expression, thus improving vascular function. These changes translated into decreased inflammation and oxidative stress within adipose tissue and decreased peroxisome proliferator-activated receptor-γ CCAAT/enhancer binding protein α, mesoderm-specific transcript, and adipocyte 2 expression and increased uncoupling protein 1 and uncoupling protein 2 expression, reflecting the effect of vascular EET overproduction on adipogenesis. The current study documents a direct link between endothelial-specific EET production and adipogenesis, further implicating the EET-heme oxygenase-1 cross talk as an important cytoprotective mechanism in the amelioration of vascular and adipocyte dysfunction resulting from diet-induced obesity.

Autonomic Blockade Improves Insulin Sensitivity in Obese Subjects

Abstract

Obesity is an important risk factor for the development of insulin resistance. Initial compensatory mechanisms include an increase in insulin levels, which are thought to induce sympathetic activation in an attempt to restore energy balance. We have previously shown, however, that sympathetic activity has no beneficial effect on resting energy expenditure in obesity. On the contrary, we hypothesize that sympathetic activation contributes to insulin resistance. To test this hypothesis, we determined insulin sensitivity using a standard hyperinsulinemic euglycemic clamp protocol in obese subjects randomly assigned in a crossover design 1 month apart to receive saline (intact day) or trimetaphan (4 mg/min IV, autonomic blocked day). Whole-body glucose uptake (Ṁgw in mg/kg per minute) was used as index of maximal muscle glucose use. During autonomic blockade, we clamped blood pressure with a concomitant titrated intravenous infusion of the nitric oxide synthase inhibitor N-monomethyl-l-arginine. Of the 21 obese subjects (43±2 years; 35±2 kg/m² body mass index) studied, 14 were insulin resistant; they were more obese, had higher plasma glucose and insulin, and had higher muscle sympathetic nerve activity (23.3±1.5 versus 17.2±2.1 burst/min; P=0.03) when compared with insulin-sensitive subjects. Glucose use improved during autonomic blockade in insulin-resistant subjects (Ṁgw, 3.8±0.3 blocked versus 3.1±0.3 mg/kg per minute intact; P=0.025), with no effect in the insulin-sensitive group. These findings support the concept that sympathetic activation contributes to insulin resistance in obesity and may result in a feedback loop whereby the compensatory increase in insulin levels contributes to a greater sympathetic activation.

Impaired Cardiovascular Structure and Function in Adult Survivors of Severe Acute Malnutrition

Abstract

Malnutrition <5 years remains a global health issue. Severe acute malnutrition (SAM) presents in childhood as edematous (kwashiorkor) or nonedematous (marasmic) forms, with unknown long-term cardiovascular consequences. We hypothesized that cardiovascular structure and function would be poorer in SAM survivors than in unexposed controls. We studied 116 adult SAM survivors, 54 after marasmus, 62 kwashiorkor, and 45 age/sex/body mass index–matched community controls who had standardized anthropometry, blood pressure, echocardiography, and arterial tonometry performed. Left ventricular indices and outflow tract diameter, carotid parameters, and pulse wave velocity were measured, with systemic vascular resistance calculated. All were expressed as SD scores. Mean (SD) age was 28.8±7.8 years (55% men). Adjusting for age, sex, height, and weight, SAM survivors had mean (SE) reductions for left ventricular outflow tract diameter of 0.67 (0.16; P=0.001), stroke volume 0.44 (0.17; P=0.009), cardiac output 0.5 (0.16; P=0.001), and pulse wave velocity 0.32 (0.15; P=0.03) compared with controls but higher diastolic blood pressures (by 4.3; 1.2–7.3 mm Hg; P=0.007). Systemic vascular resistance was higher in marasmus and kwashiorkor survivors (30.2 [1.2] and 30.8 [1.1], respectively) than in controls 25.3 (0.8), overall difference 5.5 (95% confidence interval: 2.8–8.4 mm Hg min/L; P<0.0001). No evidence of large vessel or cardiac remodeling was found, except closer relationships between these indices in former marasmic survivors. Other parameters did not differ between SAM survivor groups. We conclude that adult SAM survivors had smaller outflow tracts and cardiac output when compared with controls, yet markedly elevated peripheral resistance. Malnutrition survivors are thus likely to develop excess hypertension in later life, especially when exposed to obesity.
Abstract

Prevalence and Factors Associated With Resistant Hypertension in a Large Health Maintenance Organization in Israel

Previous assessments of the prevalence of resistant hypertension in uncontrolled blood pressure (BP) have ranged from 3% to 30%. Using real-world data, our aim was to estimate the prevalence of resistant hypertension resistant hypertension in patients belonging to the Maccabi Healthcare Services, a 2-million-member health organization in Israel. From 2010 to 2011, all hypertensive patients with ≥2 recorded BP measurements during a minimum period of 6 months were identified. Patients were considered uncontrolled if their most recent BP during the study period and their mean systolic BP or diastolic BP during a preceding period of ≥6 months were systolic BP ≥140 mmHg or diastolic BP ≥90 mm Hg, or systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg in chronic kidney disease or diabetes mellitus. Uncontrolled patients taking diuretics and ≥2 antihypertensive therapy classes at their maximal recommended dose were regarded as resistant hypertensives. A total of 172,432 patients were eligible for the study. Uncontrolled BP was found in 35.9% (n=657,110). Overall, 2.2% of the uncontrolled patients (n=1,487) were resistant hypertensives. Patients with resistant hypertension were characterized by a significantly (P<0.01) older age, higher body mass index, and multimorbidity (including dyslipidemia, diabetes mellitus, and impaired renal function) compared with patients with controlled hypertension receiving equivalent treatment. The results of this large population-based study indicate a substantially lower prevalence of resistant hypertension than previously reported. Most patients with uncontrolled BP took less than the maximal recommended antihypertensive treatment.

Maternal Parity, Fetal and Childhood Growth, and Cardiometabolic Risk Factors

Abstract

We examined the associations of maternal parity with fetal and childhood growth characteristics and childhood cardiometabolic risk factors in a population-based prospective cohort study among 9031 mothers and their children. Fetal and childhood growth were repeatedly measured. We measured childhood anthropometrics, body fat distribution, left ventricular mass, blood pressure, blood lipids, and insulin levels at the age of 6 years. Compared with nulliparous mothers, multiparous mothers had children with higher third trimester fetal head circumference, length and weight growth, and lower risks of preterm birth and small-size-for-gestational-age at birth but a higher risk of large-size-for-gestational-age at birth (P<0.05). Children from multiparous mothers had lower rates of accelerated infant growth and lower levels of childhood body mass index, total fat mass percentage, and total and low-density lipoprotein cholesterol than children of nulliparous mothers (P<0.05). They also had a lower risk of childhood overweight (odds ratio, 0.75 [95% confidence interval, 0.65–0.88]). The risk of childhood clustering of cardiometabolic risk factors was not statistically significantly different (odds ratio, 0.82 [95% confidence interval, 0.64–1.05]). Among children from multiparous mothers only, we observed consistent trends toward a lower risk of childhood overweight and lower cholesterol levels with increasing parity (P<0.05). In conclusion, offspring from nulliparous mothers have lower fetal but higher infant growth rates and higher risks of childhood overweight and adverse metabolic profile. Maternal nulliparity may have persistent cardiometabolic consequences for the offspring.

Long-Term Sympathoinhibitory Effects of Surgically Induced Weight Loss in Severe Obese Patients

Abstract

Weight loss improves insulin sensitivity and exerts sympathomodulatory effects. No data, however, are available on the effects of the weight loss induced by vertical sleeve gastrectomy on sympathetic neural drive, insulin sensitivity, and their reciprocal cross talks. In 10 severe obese hypertensives (age [mean±SEM], 54.0±2.3 years), we measured sphygmomanometric blood pressure, heart rate, body mass index, homeostatic model assessment index, plasma leptin, muscle sympathetic nerve traffic (microneurography), and baroreflex sensitivity (vasoactive drug technique). Measurements were performed 2 to 3 days before surgery and repeated 6 and 12 months after the procedure. Ten matched hypertensive obese individuals not undergoing gastrectomy served as controls. Six months after bariatric surgery, a significant (P<0.05) reduction in body mass index (−9.1±1.4 kg/m²), sphygmomanometric systolic blood pressure (−10.2±4.5 mmHg), heart rate (−11.0±2.4 bpm), homeostatic model assessment index (−3.3±1.3 AU), plasma leptin (−53.6±8.8 mug/L), and muscle sympathetic nerve traffic (−15.0±3.4 bursts/100 heart beats) was observed. The weight loss, the plasma leptin reduction, and the sympathetic inhibition were maintained after 12 months, whereas homeostatic model assessment index showed a tendency to return toward presurgery values. A significant improvement in baroreflex control of sympathetic nerve traffic was observed at 6 (+32.1%; P<0.05) and 12 months (+60.7%; P<0.01) after gastrectomy. No significant changes in the above-mentioned variables were detected in the control group. These data provide evidence that massive weight loss induced by sleeve gastrectomy triggers profound sympathoinhibitory effects, associated with a stable and significant reduction in plasma leptin levels, whereas the improvement in insulin sensitivity was attenuated with time and unrelated to the sympathoinhibition.
Role of Body Mass Index History in Predicting Risk of the Development of Hypertension in Japanese Individuals: Toranomon Hospital Health Management Center Study 18 (TOPICS 18)14

Abstract

It has not been clarified whether overall adiposity in early adulthood or at the lifetime maximum weight would confer a residual risk of hypertension after considering the risk associated with current adiposity. Study included 6121 Japanese without hypertension. The risk of developing hypertension 4 years after a baseline examination was investigated using the body mass index in the early 1920s, at the lifetime maximum, or at the baseline examination. An elevated body mass index at baseline or at the maximum rather than in the early 1920s was strongly associated with future hypertension. When compared with individuals with low body mass index both at baseline and in the early 1920s, those with an elevated body mass index at the baseline alone had an odds ratio of 1.89 (95% confidence interval, 1.58–2.27) and those with an elevated body mass index both at baseline and in the early 1920s had the highest odds ratio of 2.26 (1.76–2.89). Individuals with an elevated body mass index both at baseline and at the maximum had a 2.26-fold (1.87–2.72) increased risk of hypertension compared with those without the 2 factors. An elevated body mass index at the baseline examination weakened the favorable influence of a low body mass index in early adulthood on developing hypertension. Adding information on body mass index in early adulthood or at the maximum in addition to that at the baseline examination contributed to differentiating the risk of hypertension among Japanese, particularly among those with an elevated overall adiposity at present.

Circulating Aldosterone and Natriuretic Peptides in the General Community: Relationship to Cardiorenal and Metabolic Disease15

Abstract

We sought to investigate the role of aldosterone as a mediator of disease and its relationship with the counter-regulatory natriuretic peptide (NP) system. We measured plasma aldosterone (n=1674; aged, ≥45 years old) in a random sample of the general population from Olmsted County, MN. In a multivariate logistic regression model, aldosterone analyzed as a continuous variable was associated with hypertension (odds ratio [OR], 1.75; 95% confidence interval [CI], 1.57–1.96; P<0.0001), obesity (OR, 1.34; 95% CI, 1.21–1.48; P<0.0001), chronic kidney disease (OR, 1.39; 95% CI, 1.22–1.60; P<0.0001), central obesity (OR, 1.47; 95% CI, 1.32–1.63; P<0.0001), metabolic syndrome (OR, 1.41; 95% CI, 1.26–1.58; P<0.0001), high triglycerides (OR, 1.23; 95% CI, 1.11–1.36; P<0.0001), concentric left ventricular hypertrophy (OR, 1.22; 95% CI, 1.09–1.38; P=0.0007), and atrial fibrillation (OR, 1.24; 95% CI, 1.01–1.53; P=0.04), after adjusting for age and sex. The associations with hypertension, central obesity, metabolic syndrome, triglycerides, and concentric left ventricular hypertrophy remained significant after further adjustment for body mass index, NPs, and renal function. Furthermore, aldosterone in the highest tertile correlated with lower NP levels and increased mortality. Importantly, most of these associations remained significant even after excluding subjects with aldosterone levels above the normal range. In conclusion, we report that aldosterone is associated with hypertension, chronic kidney disease, obesity, metabolic syndrome, concentric left ventricular hypertrophy, and lower NPs in the general community. Our data suggest that aldosterone, even within the normal range, may be a biomarker of cardiorenal and metabolic disease. Additional studies are warranted to evaluate a therapeutic and preventive strategy to delay the onset and progression of disease, using mineralocorticoid antagonists or chronic NP administration in high-risk subjects identified by plasma aldosterone.

Uric Acid Promotes Left Ventricular Diastolic Dysfunction in Mice Fed a Western Diet16

Abstract

The rising obesity rates parallel increased consumption of a Western diet, high in fat and fructose, which is associated with increased uric acid. Population-based data support that elevated serum uric acids are associated with left ventricular hypertrophy and diastolic dysfunction. However, the mechanism by which excess uric acid promotes these maladaptive cardiac effects has not been explored. In assessing the role of Western diet–induced increases in uric acid, we hypothesized that reductions in uric acid would prevent Western diet–induced development of cardiomyocyte hypertrophy, cardiac stiffness, and impaired diastolic relaxation by reducing growth and profibrotic signaling pathways. Four-week-old C57BL/6J male mice were fed excess fat (46%) and fructose (17.5%) with or without allopurinol (125 mg/L), a xanthine oxidase inhibitor, for 16 weeks. The Western diet–induced increases in serum uric acid along with increases in cardiac tissue xanthine oxidase activity temporally related to increases in body weight, fat mass, and insulin resistance without changes in blood pressure. The Western diet induced cardiomyocyte hypertrophy, myocardial oxidative stress, interstitial fibrosis, and impaired diastolic relaxation. Furthermore, the Western diet enhanced the activation of the S6 kinase-1 growth pathway and the profibrotic transforming growth factor-β1/Smad2/3 signaling pathway and macrophage proinflammatory polarization. All results improved with allopurinol treatment, which lowered cardiac xanthine oxidase and serum uric acid levels. These findings support the notion that increased production of uric acid with intake of a Western diet promotes cardiomyocyte hypertrophy, inflammation, and oxidative stress that lead to myocardial fibrosis and associated impaired diastolic relaxation.
IgG Receptor FcγRIIB Plays a Key Role in Obesity-Induced Hypertension*

Abstract
There is a well-recognized association between obesity, inflammation, and hypertension. Why obesity causes hypertension is poorly understood. We previously demonstrated using a C-reactive protein (CRP) transgenic mouse that CRP induces hypertension that is related to NO deficiency. Our previous work in cultured endothelial cells identified the Fcγ receptor IIB (FcγRIIB) as the receptor for CRP whereby it antagonizes endothelial NO synthase. Recognizing known associations between CRP and obesity and hypertension in humans, in the present study, we tested the hypothesis that FcγRIIB plays a role in obesity-induced hypertension in mice. Using radiotelemetry, we first demonstrated that the hypertension observed in transgenic mouse-CRP is mediated by the receptor, indicating that FcγRIIB is capable of modifying blood pressure. We then discovered in a model of diet-induced obesity yielding equal adiposity in all study groups that whereas FcγRIIB+/− mice developed obesity-induced hypertension, FcγRIIB−/− mice were fully protected. Levels of CRP, the related pentraxin serum amyloid P component that is the CRP-equivalent in mice, and total IgG were unaltered by diet-induced obesity; FcγRIIB expression in endothelium was also unchanged. However, whereas IgG isolated from chow-fed mice had no effect, IgG from high-fat diet-fed mice inhibited endothelial NO synthase in cultured endothelial cells, and this was an FcγRIIB-dependent process. Thus, we have identified a novel role for FcγRIIB in the pathogenesis of obesity-induced hypertension, independent of processes regulating adiposity, and it may entail an IgG-induced attenuation of endothelial NO synthase function. Approaches targeting FcγRIIB may potentially offer new means to treat hypertension in obese individuals.

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