Obesity is by far the strongest risk factor for the development of type 2 diabetes. Recent clinical trials suggest that blockade of the renin-angiotensin system (RAS), either by inhibiting the angiotensin-converting enzyme (ACE) or by blocking the angiotensin type 1 (AT1) receptor, may substantially lower the risk for type 2 diabetes. Thus, in the Captopril Primary Prevention Project (CAPPP) trial, incidence of diabetes was 14% lower in the captopril group than in the conventional group, whereas, in the Heart Outcomes Prevention Evaluation (HOPE) trial, there was 34% reduction in relative risk for the development of type 2 diabetes. Similarly, in the Intervention For Endpoint Reduction in Hypertension study (LIFE), the incidence of type 2 diabetes was reduced by 25% in the losartan group, albeit versus patients treated with atenolol. The mechanism underlying this effect is unknown. Based on our recent observation that angiotensin II markedly inhibits adipogenic differentiation of human adipocytes via the angiotensin type 1 receptor and that expression of angiotensin II–forming enzymes in adipose tissue is inversely correlated with insulin sensitivity, we propose the hypothesis that blockade of the renin-angiotensin system prevents diabetes by promoting the recruitment and differentiation of adipocytes. Increased formation of adipocytes would counteract the ectopic deposition of lipids in other tissues (muscle, liver, pancreas), thereby improving insulin sensitivity and preventing the development of type 2 diabetes. (Hypertension. 2002;40:0000-0000.)

Key Words: angiotensin II diabetes adipose tissue insulin resistance obesity

Our hypothesis is supported by several observations: surgical implantation of adipose tissue reverses diabetes in lipodystrophic mice, large adipocyte size (suggesting difficulty in differentiating) is the best correlate for diabetes onset in obese Pima Indians, insulin sensitivity during overfeeding correlates with the recruitment of new adipocytes, and the in vitro yield of newly differentiated adipocytes is greater in lean than in obese subjects. Furthermore, hepatic steatosis and excess lipid in muscle and pancreas is characteristic of obese diabetics. It has also recently been suggested that the prime mechanism by which thiazolidinediones reverse insulin resistance is by stimulating the adipogenic differentiation of fat cell precursors.

Testing the Hypothesis
Testing the hypothesis that RAS blockade prevents diabetes by promoting the differentiation of adipocytes.

Hypertension is available at http://www.hypertensionaha.org DOI: 10.1161/01.HYP.0000036448.44066.53
reduce the average adipocyte size as a sign of new adipocyte

This figure summarizes our hypothesis. A, Increased formation of angiotensin II by large insulin-resistant adipocytes inhibits recruitment of preadipocytes, resulting in increased storage of lipids in muscle and other tissues, thereby decreasing insulin sensitivity. B, Blockade of the renin-angiotensin system promotes recruitment of preadipocytes, thereby increasing the number of small insulin-sensitive adipocytes. Redistribution of lipids from muscle and other tissues to adipose tissue results in improved insulin sensitivity.

explore the regulation and function of the adipose-tissue RAS, particularly regarding the issue whether large insulin-resistant fat cells do indeed produce more Ang II than smaller adipocytes. These studies will need to go beyond gene-expression analyses and should include functional assays on Ang II formation, always taking into consideration that in vitro conditions such as hypoxia may sometimes lead to results that cannot be extrapolated to the intact organism. It would also be of interest to explore whether there are regional differences in the influence of RAS blockade on adipocyte differentiation. Thus, for example, the prodifferentiating effects of thiazolidinediones have been demonstrated to be stronger on subcutaneous than on omental preadipocytes. This issue is of importance because further expansion of visceral adipose tissue by RAS blockade would be undesired, given its involvement in the metabolic and vascular complications of obesity.

Demonstrating that the profound stimulatory effect of AT₁-receptor blockade on adipogenic differentiation observed in our in vitro study is indeed present in vivo is clearly not a trivial task. One approach could perhaps be to perform fat biopsies in human subjects before and at some time point (weeks or months) during AT₁-receptor blockade. If our hypothesis is correct, AT₁-receptor blockade should perhaps reduce the average adipocyte size as a sign of new adipocyte formation in individuals without weight loss. Similar observations have been made with thiazolidinediones, where troglitazone did not change the total weight of white adipose tissues but increased the number of small adipocytes approximately 4-fold and decreased the number of large adipocytes by approximately 50%. One would also need to demonstrate that any decrease in adipocyte size by RAS blockade should result both in an improvement in ex vivo insulin sensitivity of these adipocytes and improvement of insulin sensitivity of the patient. Furthermore, AT₁-receptor blockade should result in the disappearance of lipids from muscle and liver as these are redistributed back to adipose tissue, a process that can be followed by nuclear magnetic resonance spectroscopy.

Ultimately, however, larger prospective studies would be necessary to demonstrate that induction of adipogenic differentiation by AT₁-receptor blockade is indeed related to the prevention of type 2 diabetes in high-risk individuals. Such a study would not only require a large number of subjects but also would take several years to perform.

In rodent models, Ang II has been shown to promote adipogenic differentiation of preadipocytes, the exact opposite of our finding in humans. Thus, rodent models would apparently not be suited for testing our hypothesis.

Implications for Clinical Practice

Currently, several large studies are underway to further explore the relationship between RAS blockade and the development of type 2 diabetes. Thus, the Diabetes REduction Approaches with Medication (DREAM) study will follow 4000 individuals with impaired glucose tolerance at high risk of developing diabetes who are randomized to ramipril, rosiglitazone, or placebo. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), a study in 29,000 cardiovascular high-risk patients, will also include the new development of type 2 diabetes as a secondary endpoint. If these studies confirm the preventive effect of RAS blockade on the development of type 2 diabetes, the demonstration that RAS blockade promotes the differentiation of adipocytes would provide a scientific rationale for the use of ACE inhibitors or AT₁-receptor blockers for the prevention of diabetes in high-risk individuals. Furthermore, it would also allow us to target individuals who have larger adipocytes and/or higher activities of angiotensin-forming enzymes in their adipose tissue. Such patients would, therefore, be more likely to develop diabetes than individuals with smaller adipocytes. The same may apply to individuals who have hepatic steatosis or increased myocytic lipid stores, signs of impaired adipose-tissue expansion. Recent genetic studies have identified a locus on chromosome 1 related to adipocyte size. It would clearly be of interest to explore the effect of RAS blockade on adipocyte growth and function and the development of diabetes in individuals with an apparently increased genetic predisposition for large adipocytes. [Author: The last 2 references were not cited in this paper. Per journal style, please cite or delete references.]

References


Angiotensin Blockade Prevents Type 2 Diabetes by Formation of Fat Cells
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Hypertension. published online October 7, 2002;

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/early/2002/10/07/01.HYP.0000036448.44066.53.citation

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