Adiponectin: An Adipokine Linking Adipocytes and Type 2 Diabetes in Humans

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Adipocyte-derived adiponectin is an insulin-sensitizing and antiatherosclerotic hormone, and replenishment of adiponectin in animal models ameliorated insulin resistance and atherosclerosis. In humans, recent studies have demonstrated that adiponectin level is a good predictor of developing type 2 diabetes and coronary artery disease. Decreasing level of adiponectin is caused by the interaction between genetic factors, such as single nucleotide polymorphisms in the adiponectin gene, and environmental factors, such as high-fat diet. Agents that increase blood level of adiponectin or enhance the actions of adiponectin can be an ideal medicine for ameliorating insulin resistance and type 2 diabetes.

Introduction

Several studies had reported that the adiponectin level in plasma was decreased in patients with type 2 diabetes or obesity in comparison with healthy subjects [1–3]. Therefore, it had been speculated that adiponectin may play some roles in the pathogenesis of type 2 diabetes. By experiments using animal models, we and other groups have clearly demonstrated that adiponectin has crucial roles in glucose metabolism and reduction of adiponectin action leads to glucose intolerance [4••]. In this section, we discuss to what extent and how adiponectin plays a role in the pathogenesis of type 2 diabetes in humans.

By affected sib-pair analysis, we have mapped type 2 diabetes susceptibility loci to 3q27 [5], where the adiponectin gene is located. Clinical parameters closely related to metabolic syndrome, such as body mass index (BMI) and insulin levels, were also reported to be linked concomitantly to 3q27 [6], suggesting that one locus is responsible for the pathogenesis of insulin resistance and metabolic syndrome. Moreover, our genome-wide scan for type 2 diabetes in Japanese people found a suggestive evidence of linkage between type 2 diabetes and 3q27. Given the fact that there has been the small number of chromosomal regions (*eg,* 1q and 20q) that consistently showed linkage to type 2 diabetes or its related quantitative trait in different populations, 3q27 may harbor a susceptibility gene common to different ethnic groups and it seems to be promising to search for type 2 diabetes genes in this region.

We have previously generated and investigated peroxisome proliferator-activated receptor-γ (PPAR-γ) (+/-) mice and found that these mice were protected from high fat–induced obesity and insulin resistance [7]. Very interestingly, expression level of the adiponectin gene in PPAR-γ (+/-) mice was significantly increased compared with wild-type mice, suggesting that adiponectin is an insulin-sensitizing hormone [8]. In fact, replenishment of adiponectin in a model animal of type 2 diabetes ameliorated insulin resistance significantly. Therefore, we screened single nucleotide polymorphisms (SNPs) in the adiponectin gene and performed an association study to investigate the role of the adiponectin gene in the pathogenesis of insulin resistance and type 2 diabetes in humans [9]. We detected 10 relatively frequent polymorphisms in the adiponectin gene [9]. There was significant difference in the distribution of genotypes of SNPs located in intron 2 at 276 bp downstream from the translational start site (thus designated as "SNP276") between type 2 diabetic and nondiabetic subjects. The subjects with the G/G genotype of SNP276 were at an approximately two times increased risk for type 2 diabetes compared with those having the T/T genotype [9]. Moreover, the plasma adiponectin levels were lower in the subjects with the G/G genotype, suggesting that genetically inherited decreases in adiponectin levels predispose subjects to insulin resistance and type 2 diabetes. It is of note that more than 40% of Japanese people have an "at-risk" genotype that predisposes subjects to genetically decreased adiponectin levels and are thus susceptible to type 2 diabetes. This may be an alert to our society, because high-fat diet may have a disastrous effect on glucose metabolism by furthermore decreasing the adiponectin levels in those subjects [10].

A report by Comuzzie *et al.* [11] supports the notion that blood adiponectin concentration is regulated by genetic factors, including the polymorphism in the adiponectin gene itself. They found that genetic heritability of adiponectin is calculated up to 46%, indicating that adiponectin is regulated substantially by some genetic factors. Subsequently performed genome-wide scans have mapped loci affecting adiponectin levels to several chromosomal regions, including 3q27, although the peak was not the highest one [11]. In German and American Caucasians, the SNP276, either independently or as a haplotype, together with the SNP45 in the exon 2, was associated with obesity and insulin resistance [12,13]. However, the association of these two SNPs with type 2 diabetes and insulin resistance was not seen in French Caucasians. Instead, two SNPs in the promoter region of the adiponectin gene, SNP-11377 and SNP-11391, were significantly associated with hypoadiponectinemia and type 2 diabetes in French Caucasians [14,15]. These results may suggest that the genetic defects of SNPs in the adiponectin gene are influenced by genetic backgrounds and environmental factors in different ethnic populations. Altogether, these data strongly support the hypothesis that adiponectin plays a pivotal role in the pathogenesis of type 2 diabetes. Further study, such as meta-analysis including as much negative reports as possible and functional analysis, will be needed.

Mechanism of Insulin Sensitization by Adiponectin: Human Study

Previous studies indicated that intramyocellular lipid (IMCL) content is a strong marker of insulin resistance and this relationship is independent of the percentage of total fat and adiposity [16,17]. A close inverse relationship between plasma adiponectin level and IMCL content in the skeletal muscle has been shown, which is consistent with the data from animal models of diabetes, indicating that adiponectin acts on the skeletal muscle tissue to increase influx and combustion of free fatty acids, thereby reducing muscle triglyceride content. Modulatory effects of adiponectin on glucose transport are, at least in part, mediated via its effect on the IMCL content because the relationship between adiponectin and glucose transport was completely lost after controlling for IMCL content.

In a cross-sectional study including obese and lean men and women, the inverse relationship between plasma adiponectin and visceral fat (measured by computed tomography scan) was significantly stronger than that with subcutaneous fat [18]. One explanation is that adiponectin is primarily produced by visceral adipose tissue, but that large triglyceride-filled visceral adipocytes produce less adiponectin. It has been reported that omental adipocytes secrete more adiponectin than adipocytes isolated from subcutaneous fat. The known insulin-sensitizing actions of adiponectin suggest that reduced adiponectin production may contribute to the well-known relationship between visceral fat deposition and insulin resistance.

Adiponectin Protects Subjects from Type 2 Diabetes: Prospective Study

Several cross-sectional studies have reported that adiponectin levels were decreased in subjects with type 2 diabetes and that adiponectin levels were inversely correlated with insulin resistance [1–3]. However, there has been no study that investigated whether adiponectin protects subjects from diabetes and the extent of risk of developing diabetes in subjects with hypoadiponectinemia.

Recently, two matched case-control studies in subjects recruited from a large cohort have been performed to investigate the protective effect of adiponectin against diabetes prospectively. One study is performed in German Caucasians with mild obesity. Increasing concentrations of adiponectin were associated with a substantially reduced relative risk of type 2 diabetes, even after adjustment for possible confounding factors such as BMI [19••]. The risk reduction rate was 8.1% per microgram per milliliter of adiponectin. Subjects with the highest quartile of adiponectin had as much as 70% lower risk of developing type 2 diabetes compared with the lowest quartile of adiponectin. The other study was performed in severe obese subjects in Pima Indians, who have the highest known prevalence of obesity and type 2 diabetes in the world, to assess the role of adiponectin independent of effects of obesity [20]. Subjects with high concentrations of adiponectin were 40% less likely to develop type 2 diabetes than those with low concentrations after adjustment for BMI. These two results clearly indicated that adiponectin has a substantial role in the pathogenesis of type 2 diabetes, and that adiponectin could be used as an indicator of risk of type 2 diabetes, in addition to the established risk parameters, such as BMI.

The effect of adiponectin on the risk of type 2 diabetes seems to be comparable among different ethnic groups. Large prospective studies are needed to be performed before the measurement of adiponectin can be applied to daily clinical use. As to the SNPs in the adiponectin gene, a cohort study in which 4500 French-Caucasian subjects were enrolled and followed up for 3 years reported that the polymorphisms in the adiponectin gene [21], one of which is in the promoter and the other is located in the exon 2, are associated with the prospective risk of hyperglycemia in apparently healthy subjects at baseline. In addition to the genetic polymorphisms of the adiponectin gene, the baseline adiponectin level itself also had a predictive value on the risk of developing hyperglycemia. Conditional logistic regression showed that the SNPs in the adiponectin gene and baseline adiponectin levels were independently associated with the onset of hyperglycemia. This result is consistent with the notion that susceptibility to type 2 diabetes is affected by both genetic and environmental factors. Genetic polymorphisms affecting the expression levels and functions of adiponectin and lifestyle, which decrease plasma adiponectin level through obesity, cooperatively predispose subjects to insulin resistance and type 2 diabetes.

Adiponectin Has Substantial Roles in the Pathogenesis of Coronary Artery Disease

Adiponectin is inversely correlated with cardiovascular risk factors, such as blood pressure, heart rate, and total and low-density lipoprotein cholesterol and triglyceride levels [22,23], and is positively correlated with high-density lipoprotein cholesterol levels [23,24]. Therefore, adiponectin protects subjects from atherosclerosis through its ameliorative effect on glucose and lipid metabolism. Overexpression of adiponectin protected apolipoprotein E–deficient mice from atherosclerosis, although transgenic mice had comparable levels of blood pressure, cholesterol levels, and insulin, suggesting that adiponectin has a direct antiatherogenic effect independently from its actions on traditional risk factors of atherosclerosis [25].

A recent study to assess the association between plasma adiponectin levels and risk of myocardial infarction (MI) in humans supports this notion that adiponectin protects from cardiovascular diseases both directly and indirectly [26]. Subjects in the highest quintile of adiponectin levels had a significantly decreased risk of MI compared with the lowest quintile of adiponectin levels. After adjustment for surrogate parameters of risk factors, such as hemoglobin A_{1c} and low- and high-density lipoprotein cholesterol levels, the risk reduction by high adiponectin concentration was preserved. Moreover, circulating adiponectin levels have been reported to be positively associated with arterial vasodilatation in response to nitroglycerin, a measure of endothelium-independent vasodilatation, which is independent of a correlation with insulin sensitivity. When conventional cardiovascular risk factors were present, such as impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes, no significant associations between endothelial or vascular dysfunction and adiponectin were found. Future studies are needed to be performed to depict the molecular mechanisms in which adiponectin exerts a direct antiatherosclerotic effect.

Medication and Lifestyle Modification Ameliorate Insulin Resistance and Type 2 Diabetes Through Increasing Adiponectin Levels

If low adiponectin level has a major role in the development of lifestyle-related diseases, does medication or lifestyle intervention increase adiponectin levels? Several studies in humans reported that circulating adiponectin levels increase after weight loss due to diet therapy [27,28]. The low plasma adiponectin concentrations in morbidly obese subjects are also reported to be normalized after weight loss induced by gastric bypass surgery [29]. In patients with stable weights, those subjects with the lowest presurgical adiponectin levels lost the most weight after surgery and the subjects exhibiting the largest increases of plasma adiponectin were the most insulin sensitive after surgery-induced weight loss. A possible explanation for the paradoxic reduction of adiponectin in obese subjects and the increase after weight loss is that adiponectin may be primarily produced by visceral fat, as suggested by one study of human adipocytes in vitro, but that large visceral adipocytes with greater triglyceride stores produce less adiponectin than small adipocytes. Because large adipocytes are less insulin sensitive, it is possible that the insulin sensitivity of adipocytes is also a determinant of adiponectin production.

Humans with severe insulin-resistant diabetes due to dominant-negative mutations that inactivate PPAR-γ have very low circulating adiponectin levels [30]. Thiazolidinediones (TZDs), agonists of PPARs, increase adiponectin expression and circulating levels in rodents and plasma adiponectin levels in nondiabetic and type 2 diabetic patients [31]. Given that the amelioration of insulin sensitivity by TZD treatment is related to the increase of circulating adiponectin, the effect of TZDs to increase whole-body insulin sensitivity and to protect against cardiovascular disease could be mediated, at least partly, by increased adiponectin production [31].

It has very recently been reported that pioglitazone induces marked increase in the (high-molecular-weight [HMW]) adiponectin, which correlated strikingly with the improved hepatic insulin action [32]. Moreover, amelioration of insulin sensitivity in the liver preceded significant changes in plasma glucose levels and insulin sensitivity in skeletal muscle, suggesting that increased levels of HMW adiponectin are well correlated with enhanced suppression of endogenous glucose production from the liver but not with increased insulin-stimulated glucose uptake in the skeletal muscle. It is important that relative increases in HMW adiponectin multimers may correlate more strongly with improved insulin sensitivities than total adiponectin levels. Future study will be needed to investigate whether measurement of HMW or ratio of HMW to total adiponectin level may be a better indicator of insulin sensitivity and responsiveness to treatment than total adiponectin levels.

Mutations in the adiponectin, G84R, G90S, Y111H, R112C, and I164T, are related to the diabetic and hypoadiponectinemic phenotype [33]. A close relationship between those mutants and impaired multimerization was observed [34], which was parallel with diabetes or hypoadiponectinemia and mutants without overtly abnormal phenotype showed normal multimerization. Missense mutation, in which the I164T mutation was the most frequent, was accompanied by marked hypoadiponectinemia. Subjects with the I164T mutation were accompanied by hypertension or hyperlipidemia, impaired glucose metabolism, and coronary artery disease. Measurement of HMW adiponectin may be useful to diagnose genetically impaired multimization and hypoadiponectinemia, which is involved in the pathogenesis of metabolic syndrome and cardiovascular diseases, although the frequency of such mutations is low.

Toward Personalized Medicine for Metabolic Syndrome and Cardiovascular Diseases

Metabolic syndrome and cardiovascular disease are multifactorial diseases, in which multiple genetic and environmental factors coordinately exert effects on the onset and development of the diseases. There is plenty of evidence indicating high-fat diet is the major cause of metabolic syndrome. In concordance with rapid increase in fat consumption recently in Japan, the number of people with diabetes is increasing rapidly to be estimated around 7.4 million by the report of the national survey in 2003. An analysis taking the environmental factors into account, such as eating habit and physical activities, is needed to be performed to predict the onset of metabolic syndrome accurately.

We now use an electronic medical record system, which gathers and accumulates various clinical information generated in vast quantity in day-to-day practice. Using data-mining tools, we think it is possible to extract interactions between genetic and environmental factors predisposing subjects to metabolic syndrome and cardiovascular diseases. Providing clinical services to determine these genotypes would be of great help for each individual to make a plan for tailor-made health promotion.

Conclusions

There is plenty of evidence that adiponectin has major roles in the pathogenesis of type 2 diabetes and atherosclerosis. Well-designed studies have demonstrated that plasma adiponectin level is a good predictor of developing diabetes and MI. However, factors that should be considered in assessing clinical validity, such as sensitivity and predictive value, need to be tested before adiponectin is applied in clinical use. The roles of the two adiponectin receptors [35], ADIPOR1 and ADIPOR2, are now under intensive investigations. A detailed characterization of the adiponectin-signaling cascade in tissues involved in the pathogenesis of type 2 diabetes and vascular tissues will potentially provide insight into novel therapeutic approaches for diabetes and cardiovascular diseases.

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