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Diabetes, Obesity and Erectile Dysfunction: Field Overview and Research Priorities

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Abstract

Purpose—We provide an overview of basic, clinical and epidemiological research in the field of erectile dysfunction and important research priorities presented at the 2009 National Institute of Diabetes and Digestive and Kidney Diseases symposium on Urological Complications of Diabetes and Obesity.

Materials and Methods—Experts in molecular biology, physiology, pharmacology, clinical trials, epidemiology and urological surgery highlighted current knowledge on erectile dysfunction associated with diabetes mellitus and obesity.

Results—Predictable associations between erectile dysfunction, and poor diabetic control and modifiable risk factors, including body mass index, have not yet been translated into randomized trials in the United States. The relationship between erectile dysfunction and metabolic syndrome, and surrogate markers for erectile dysfunction requires further investigation. Basic research aimed at discovering disease mechanisms and therapeutic targets has focused on autonomic neuropathy, vascular dysfunction, smooth muscle contractile function and matrix. However, significant gaps exist in regard to the integration of molecular, cellular and functional data. Animal models of type 2 diabetes and obesity associated erectile dysfunction require investigation because most basic science studies have used rodent models of type 1 diabetes.

Conclusions—Studies are needed to synthesize a systems biology understanding of erectile function/dysfunction, and characterize and disseminate rodent models of erectile dysfunction associated with type 2 diabetes and obesity. Clinical studies are needed of promising intervention and prevention strategies. Leveraging existing and future cohort phenotypes, and biological samples is needed for risk factor analysis, biomarker discovery and genome wide association studies.

Keywords

penis; impotence; diabetes; obesity; epidemiology

THE prevalence of diabetes is rapidly increasing in the United States and the disease has a high economic cost.¹ Complications of diabetes initiate 18% to 25% of all inpatient hospital admissions and represent a major concern for patients and physicians. Obesity may carry an even larger burden of disease due to the alarming increase in its prevalence.²

Diabetes and increased body mass index independently increase the risk of ED. Together these conditions account for more than 8 million ED cases in the United States.³ This prevalence is expected to increase substantially because earlier onset of pathophysiological processes associated with hyperglycemia and adiposity will amplify the risk. The total direct cost for the evaluation of ED treatment in the United States is estimated to be \$400 million,³ of which approximately \$100 million are attributable to diabetes and obesity associated ED. These costs exclude the potential pharmacy contribution to the financial burden of ED. If all 8 million men with diabetes and obesity related ED sought evaluation and oral pharmacological treatment, based on current models the yearly cost of drug treatment alone would exceed \$4 billion.³

Clinical and basic science studies have identified factors that increase the likelihood of ED but none have been translated into strategies to decrease the incidence of new cases. Furthermore, pharmacological therapy is less effective in men with diabetes and does not prevent progression to irreversible ED. Well developed epidemiological, clinical and fundamental research points to a combined metabolic, neurogenic and vasculogenic etiology for ED in patients with T1D4 but current knowledge about ED mechanisms in patients with T2D and obesity is less comprehensive.⁵ Importantly long-term observational studies of men with T2D and obesity are lacking, federal and foundation funding has long emphasized studies of T1D, and animal models to investigate T2D mechanisms have only recently gained attention. Because noninsulin dependent diabetes (T2D) accounts for 90% to 95% of adult cases in the United States, closing this knowledge gap is important. We provide a summary of topical research activity in diabetes and obesity associated ED, a focus of a 2009 National Institute of Diabetes and Digestive and Kidney Diseases symposium on Urological Complications of Diabetes and Obesity. This brief overview highlights important basic science, epidemiology and clinical investigations, and enumerates research priorities in the field.

EPIDEMIOLOGICAL OBSERVATIONS

Cross-sectional and longitudinal epidemiological studies demonstrate that diabetes and several measures of adiposity significantly and independently increase the risk of ED. Multivariate analyses of several population based cohorts show that of all risk factors diabetes imparts the highest risk for ED with an age adjusted relative risk of 1.3 to 3 depending on diabetes type.⁵⁻⁷ In men with diabetes ED begins earlier than in the general population, and is associated with decreased health related quality of life and decreased success of all known ED treatments, including oral pharmacological therapy and penile implants. An association exists between glycemic control and ED in men with diabetes, in that patients with poor control are at 2 to 5-fold increased risk for ED compared to patients with good control.^{8,9} Other diabetic complications associated with ED in longitudinal and cross-sectional studies were summarized previously, including diabetes duration, limb loss, retinopathy, nephropathy and untreated hypertension.⁴

Body weight and adiposity are significantly associated with ED.^{3,6,7} Convergent data from the Health Professionals Follow-up Study, the National Health and Nutrition Examination Study and MMAS show that compared to men with a BMI of less than 25 kg/m² the odds of ED are higher in men with a BMI of 25 to 30 kg/m² and even higher in men with a BMI of greater than 30 kg/m². The risk is increased 1.5 to 3-fold. Other measures of adiposity, including the waist-to-hip ratio and abdominal circumference, are also independently associated with ED risk.

While low levels of physical activity are often associated with obesity, they impart an additional risk for ED. Independent of BMI, physically active men (greater than 16 MET hours per week of exercise) are at 30% lower risk for ED than sedentary men. Also, increases in physical activity are independently associated with a lower risk of incident ED. In men without ED at

baseline who were followed for 8 years in MMAS the lowest risk of ED was in those who were sedentary at baseline and became physically active (200 kcal or greater per day of activity), whereas the highest risk was in men who were sedentary at each time.⁷

It has become axiomatic that ED shares important risk factors with cardiovascular disease. Results from a longitudinal prostate cancer prevention study showed that incident ED is associated with a higher risk of subsequent cardiovascular events.¹⁰ More recently a similar association was noted in men with T2D and ED.¹¹ Data from MMAS show that ED predicts subsequent metabolic syndrome in men with BMI less than 25 kg/m², a group otherwise considered at low risk for cardiovascular disease (multivariate adjusted RR 2.09; 95% CI 1.09, 4.02).¹² ED also predicts cardiovascular disease events and increased cardiovascular mortality, confirming earlier cited reports.¹³

Hypogonadism may be a link between T2D/metabolic syndrome and ED. Men with ED and T2D have a higher prevalence of hypogonadism,¹⁴ and low testosterone correlates with poor glycemic control and worsening ED.¹⁵ Visceral adiposity and general obesity prevalent in men with T2D and metabolic syndrome can directly impact testosterone. Increased aromatase in adipose tissue can lead to increased androgen conversion from testosterone to estrogens. An association between increased BMI, and waist circumference and hypogonadism has been established in men with T2D.¹⁵⁻¹⁷ Hypogonadism is also associated with other components of metabolic syndrome, such as altered lipid status. Hypogonadal patients with T2D ED have increased triglycerides and lower HDL cholesterol.¹⁴

Insights From Clinical Trials

Robust drug discovery programs for ED helped move the field forward in 2 important ways. Clinical trials data in specialized populations, including those with diabetes, provided material for potential future biomarker discovery. The second way is the development and use of well validated outcome measures, including IIEF, to determine ED prevalence, incidence and risk factors in epidemiological studies, and response to treatment in clinical trials.

In a significant number of clinical trials groups have investigated the efficacy of PDE5-I for diabetes associated ED. The proportion of men with diabetes who experience improvement in ED by PDE5-I administration was 57% to 74% in 2 pivotal trials.^{18,19} A recent Cochrane Review showed that PDE5-I improved ED in diabetic men.²⁰ However, these trial results are not fully generalizable to clinical practice. Selection bias at enrollment, and the exclusion of men with poor glycemic control and more severe diabetic complications make it likely that in the general population PDE5-I would be less efficacious than in clinical trials.

Given the limitations of oral pharmacotherapy and the unrelenting increase in the prevalence of ED, expenditures for ED will become unsustainable. Thus, strategies have been sought to reverse or improve ED.

Glycemic Control and ED Risk

Although a number of studies show an association between poor glycemic control and an increased risk of ED, to our knowledge no study has been specifically designed to determine whether intensive improvements in glycemic control would have a beneficial effect on erectile function. The EDIC (Epidemiology of Diabetes Intervention and Complication Study) is a longitudinal cohort followup study for the Diabetes Control and Complication Trial, in which patients with T1D were randomized to conventional or intensive glycemic control. In an ancillary study of urological complications, the Uro-EDIC, the effect of intensive glycemic control on the subsequent risk of ED was assessed.²¹ ED was measured using IIEF in a subset of 291 men with a 1 to 5-year history of diabetes and no microvascular complications (primary

prevention), and another group of 280 with a 1 to 15-year history of diabetes with minor complications (secondary intervention). In analyses comparing men initially randomized to intensive vs conventional therapy there was no difference in ED in the primary prevention cohort (OR 1.24; 95% CI 0.68, 2.28). In the secondary intervention cohort ED was significantly less likely in those assigned to intensive control than in those assigned to conventional therapy (OR 0.33; 95% CI 0.18, 0.60).

In men with T2D only limited data have been reported on risk reduction strategies for ED. The 41 men with T2D in a behavioral and pharmacological intervention for cardiac risk reduction experienced significant improvements in hemoglobin A1c, diastolic blood pressure and total cholesterol during 4 weeks of intervention.²² Changes in systolic and diastolic blood pressure, and a decrease in or maintenance of hemoglobin A1c below 7.0% were significantly associated with a change on IIEF-5.

A limitation of these 2 studies is that neither was designed specifically to test the hypothesis that ED would improve with the intervention. Future studies including validated ED measurements, adequate sample size and important potential confounders would have the potential to more definitively reveal a benefit to intensive glycemic control in men with poorly controlled diabetes and ED or those at high risk for its development.

Lifestyle Intervention

A number of lines of investigation suggest that weight loss by bariatric surgery or intensive diet and exercise programs improves erectile function in obese men with ED.²³⁻²⁶ Lifestyle interventions improve endothelial function and NO bioavailability, and may have beneficial effects on ED via this mechanism. Weight loss may also improve ED through other mechanisms, including decreased inflammation, increased testosterone, and improved mood and self-esteem.

The strongest evidence supporting the benefit of lifestyle intervention for ED is from the randomized, controlled trial of 110 obese men by Esposito et al in Italy.²⁴ Men with a mean BMI of 36 kg/m² and moderate ED (mean IIEF-EF score 13.7) were randomly assigned to a lifestyle intervention including exercise and weight loss or to an educational control. Notably men with hypertension, diabetes or hyperlipidemia were excluded from study and participants were not seeking help for ED. During 2 years the intervention group lost more weight than controls (15 vs 2 kg) and had greater increases in physical activity (195 vs 84 minutes per week). Erectile function improved in the intervention group (IIEF-EF score 13.9 to 17.0, $p < 0.001$) but did not change in the control group (mean score 13.5 to 13.6, $p = 0.89$). Moreover, 30% of participants in the intervention group recovered normal erectile function (IIEF-EF score 22 or greater) compared to 5% of controls. Improved erectile function correlated significantly with the amount of weight loss and increased activity with each independently explaining about 25% of the variance of change in the IIEF score. Men in the intervention group also had significantly greater improvement in endothelial function (blood pressure and platelet aggregation response to L-arginine), decreases in C-reactive protein and improvement in standard cardiovascular risk factors. Changes in C-reactive protein but not in the surrogate markers of endothelial function were related to changes in IIEF.

Future clinical trials are needed to determine whether lifestyle intervention should be recommended as first line therapy in obese men with ED and identify those most likely to respond to lifestyle changes. Important additional studies are also needed to determine whether diabetes changes the treatment response to weight loss. Any treatment approach that can address these health problems simultaneously would be important for public health.

BIOMARKER DISCOVERY

Numerous markers of systemic inflammation, oxidative stress and endothelial cell injury have been investigated as biomarkers of endothelial dysfunction and many have also been proposed as surrogate markers of ED. In a cross-sectional analysis of a subset of the Health Professionals cohort select biomarkers for endothelial function, thrombosis and dyslipidemia but not for inflammation were associated with the degree of ED.²⁷ In an analysis of men with ED and no overt cardiovascular risk factors investigators found that endothelin-1 independently predicted ED.²⁸ Preliminary reports from a number of investigators suggest potential targets for further investigation in diabetes associated ED cases, including endothelial microparticles, monocyte activation and various endothelial cell adhesion molecules.²⁹⁻³¹ A small randomized, controlled trial in men with T2D and ED showed that short-term continuous sildenafil treatment caused enhanced systemic endothelial function and it remained so after discontinuing sildenafil.³² However, there was no associated improvement in long-term erectile function. To our knowledge no large-scale, longitudinal, prospective studies have validated a particular assay for identifying ED or tracking patients at high risk.

BASIC SCIENCE

Abnormal carbohydrate metabolism and hyperglycemia underlie T1D and T2D. However, T1D and T2D differ significantly in other characteristics, including insulin and BMI status as well as cytokine and lipid profiles. Although most diabetes related ED develops in men with T2D,³³ most basic science studies have examined mechanisms of ED in animal models of T1D. To date approximately a dozen studies have used animal models of T2D. However, a vast array of rodent models of T2D are available for study, including the obese ZDF, the BBZ/WOR rat and the Otsuka Long-Evans Tokushima Fatty rat.³⁴⁻³⁷ Mouse models are also commonly available for study, including high fat diet fed, Tsumura Suzuki Obese Diabetes, KK, New Zealand obese, *ob/ob* and *db/db* mice,³⁸⁻⁴⁰ of which the latter 2 result from leptin deficiency and insensitivity, respectively. These animals show a combination of hyperglycemia, often with concurrent insulin resistance, hyperlipidemia and obesity, representing the human T2D phenotype. Nonetheless, erectile function has only been characterized in a few of these available models and further study is warranted. Importantly animal models of increased BMI without an overt diabetes phenotype must also be investigated to elucidate pathophysiological processes specific to obesity. Particular attention to adipokine mediated mechanisms of ED are warranted based on initial studies showing that tumor necrosis factor- α may have a role in erectile response impairment.⁴¹

Studies of impaired erectile function in animal models of T2D show various potential underlying mechanisms for this disorder. Pathological functions include hypogonadism, vascular dysfunction and veno-occlusive disorders, as reviewed previously.⁴² Although neuropathy is a predominant underlying feature of ED in animal models of T1D, the role of nonadrenergic noncholinergic neurogenic dysfunction in T2D associated ED cases is still debated. Vascular signaling abnormalities including endothelial dysfunction (impaired relaxation of cavernous tissue to endothelium dependent stimuli) as well as a hypercontractile response have a role in animal models of T2D.⁴³ Endothelial dysfunction can be described as impaired NO bioavailability resulting from decreased endothelial NO synthase expression or activity, or increased NO scavenging. Indeed, attenuated endothelium dependent vasoreactivity was noted in various animal models of T2D, including the high fat diet fed and the *db/db* mouse as well as the ZDF rat.⁴⁴⁻⁴⁶

NO scavenging through increased oxidative stress also likely underlies ED in T2D cases. Hypercontractility may result in a high level of endogenous tone to be overcome by dilatory stimulus and in various studies it had a potential role in T2D models, including the *db/db* mouse

and the ZDF rat.⁴⁴⁻⁴⁶ A veno-occlusive disorder was also suggested by studies in several T2D models.^{42,44,47} Changes in matrix components such as elastin and collagen may underlie this disorder, as identified by various groups.^{42,44,47} Interestingly although some mechanisms that may mediate ED in T2D animals are similar to those in T1D models, there are also notable differences in some underlying pathological conditions, such as nerve mediated signaling and vasoreactive changes. These findings were further discussed previously⁵ and must be replicated in additional animal models of T1D and T2D. However, if this evidence from various basic science studies translates to patients with diabetes, it could have far-reaching implications for caution in clinical study design and specificity of treatment selection between T1 and T2D cohorts.

It is clear that a large need exists for future basic science study in animal models of T2D. Despite an abundance of available animal models there is a significant lack of basic science investigations of mechanisms of ED in T2D cases.⁴² Furthermore, integrating the vascular, neuropathic, hormonal and metabolic components of the abnormal penile erectile response to T2D requires a broader, systems biology approach to achieve a cohesive synthesis. Future studies characterizing the various animal models featuring combinations of hyperglycemia, hyperlipidemia, hyperinsulinemia and obesity would expand our understanding of the contribution of these processes to diabetic ED.

CONCLUSIONS

Significant advances in our understanding of diabetes and obesity associated ED have come from epidemiological studies, clinical trials and research laboratories. Despite the advent of effective oral pharmacotherapy the increasing burden of disease requires new treatment and prevention strategies for ED. The areas of highest priority for future research are 1) clinical studies of promising intervention and prevention strategies for weight reduction and physical activity to treat ED in overweight and obese men, and intensive glycemic control to improve ED in men with poorly controlled diabetes, 2) integrative molecular, cellular and functional studies that synthesize a systems biology understanding of erectile function and diabetic ED, 3) characterization and dissemination of rodent models of T2D and obesity associated ED, and 4) ancillary studies to strengthen existing and future cohort phenotypes and biological samples for risk factor analysis, biomarker discovery and genome wide association studies.

Abbreviations and Acronyms

BMI	body mass index
CRP	C-reactive protein
ED	erectile dysfunction
IIEF	International Index of Erectile Function domain
IIEF-EF	IIEF-erectile function
MMAS	Massachusetts Male Aging Study
NO	nitric oxide
PDE5-I	phosphodiesterase type 5 inhibitor
T1D	type 1 diabetes
T2D	type 2 diabetes
ZDF	Zucker rat

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