Erectile dysfunction

The benefits of lifestyle change in obese men with erectile function

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Obesity is an epidemic and shows no sign of abating. In consequence, we are observing parallel increases in the development of diabetes and vasculopathy. These intrinsic abnormalities of the circulation are integrally linked to endothelial dysfunction, which in turn is associated with the development of erectile dysfunction (ED).

In keeping with other disease processes, we have seen an exponential rise in successful pharmaceutical products that can tackle each component of this quartet (obesity, diabetes, cardiovascular disease and ED). Whilst these developments must be applauded, this should not deter from our efforts to prevent or retard disease through lifestyle measures.

It is surprising to think that there is a relative paucity of data on the outcome of the most widely available and cheapest approach to weight loss (lifestyle measures). It is refreshing, therefore, to see Esposito et al contributing a further dimension to the benefits of lifestyle-induced weight loss. In their well conducted randomised single-blind trial, they demonstrate that significant improvements in erectile function can be achieved through weight loss, associated with a concomitant improvement in surrogate markers of vascular risk. After two years, the intervention group showed a drop in body mass index from 36.9 to 31.2 kg/m^2 (nearly 15 % weight loss) associated with a significant improvement in subjective analysis of ED. One-third of these patients reported return of normal potency. Thus, there is added incentive for many men with diabetes to lose weight, since ED is perhaps the most common complication in this patient group.

This study also lends further credibility regarding the need to develop structured healthcare networks that provide long-term support to individuals wishing to lose weight through non-pharmacological approaches, in tandem with the development of smoking cessation services. The benefits of weight loss would seem to extend beyond just diabetes and cardiovascular disease.

JOURNAL OF MEDICINAL CHEMISTRY

Potential ED drug: dopaminergic agent with novel action

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 Selective dopaminergic D_4 agonists have been shown in animals to be highly efficacious in facilitating penile erections, but without the side-effects of other known dopaminergic classes.

2 2-(4-Pyridin-2-ylpiperazin-1-ylmethyl)-1*H*-benzimidazole (ABT-724) is particularly potent and selective, as was shown in rats in vivo.

3 With ABT-724, penile erections were induced in 77 % of rats at a 0.03 µmol/kg dose – three times as potent as apomorphine (91% response rate at 0.1 µmol/kg) – due to selective activation of central D_4 receptors rather than peripheral D_4 receptors.

4 In animal studies, ABT-724 was devoid of central nervous system side-effects. Significantly there was no nausea or emesis, even at doses of 3 µmol/kg. Therefore, for erectogenic effect there is >100-fold window of selectivity for drug doses.

5 This paper also describes in vivo and in vitro profiles, the structure-activity of the parent benzimidazole series leading to ABT-724 and structural features leading to selective D_4 agonism.

Cowart M, Latshaw SP, Bhatia P, et al (2004) Discovery of 2-(4-Pyridin-2-ylpiperazin-1-ylmethyl)-1H-benzimidazole (ABT-724), a dopaminergic agent with a novel mode of action for the potential treatment of erectile dysfunction. *Journal of Medicinal Chemistry* **47**: 3853–64

JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION

Effect of lifestyle change on ED in obese men

Readability	✓ ✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 Several modifiable lifestyle factors are associated with erectile function maintenance.

2 This study aimed to ascertain the effect of increased physical activity and weight loss on erectile function.

3 Over a three-year period, 110 obese men with a body mass index (BMI) of ≥30 and ED (score ≤21 on the International Index of Erectile Function [IIEF]) were studied.

4 The 55 men in the control group were given general information on exercise and healthy food choices. In the intervention group (n=55), advice was given on how to reduce caloric intake and increase physical activity, in order to achieve ≥10% loss of their total body weight.

5 BMI decreased significantly after two years in those in the intervention group from a mean of 36.9 to 31.2 compared to 36.4 to 35.7 in the control group (p=0.001). Mean activity levels increased more in the intervention group.

6 The IIEF score improved in the intervention group (p=0.001) but remained stable in the control group – three men in the control group 17 men in the intervention group reported an IIEF score of ≥22.

7 BMI, C-reactive protein and physical activity changes were shown by multivariate analysis to be independently associated with changes in IIEF score.

8 Sexual function improved in approximately one-third of obese men with ED due to lifestyle changes.

Esposito K, Giugliano F, Di Palo C, et al (2004) Effect of lifestyle changes on erectile dysfunction in obese men. *Journal of the American Medical Association* **291**: 2978–84

'ED seems to be strongly and independently associated with angiographically verified silent CAD in uncomplicated type 2 diabetic patients at relatively low risk for CAD.'

CIRCULATION

Relationship between ED and silent MI in type 2 diabetes

Readability	✓ ✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 There is an association between coronary artery disease (CAD) and ED. Asymptomatic or silent CAD is particularly prevalent in people with diabetes. Currently it is not known what the prevalence of ED in patients with diabetes who have asymptomatic CAD is.

2 This study aimed to determine whether there is a link between ED and asymptomatic CAD in patients with type 2 diabetes.

3 ED prevalence was assessed in 260 men with diabetes: 133 with uncomplicated diabetes and asymptomatic CAD verified by an angiogram; 127 without myocardial ischaemia, verified by stress echocardiography, exercise ECG and 48-hour ambulatory ECG.

4 The IIEF-5 questionnaire was used to assess the men's erectile function, the results of which showed that there was a significantly higher percentage of men with silent CAD (33.8 %) who had ED, compared to those without (4.7 %), p=0.000.

5 Multiple logistic regression analysis was performed and silent CAD was used as the dependent variable. The predictive variables used were: diabetes duration, age, hypertension, family history of CAD, microalbuminuria, smoking, HbA_{1c}, BMI, cholesterol, lipoprotein(a), apolipoprotein(a) polymorphism, autonomic dysfunction, LDL cholesterol, HDL cholesterol and triglyceride levels.

6 Analysis showed that the following were significant predictors of silent CAD in people with diabetes: ED, smoking, microalbuminuria, apolipoprotein(a) polymorphism, LDL and HDL cholesterol. The most efficient predictor of silent CAD from these factors was ED (odds ratio 14.8; 95 % confidence interval 3.8 to 56.9).

7 In men with seemingly uncomplicated diabetes, there was a strong independent association between ED and asymptomatic CAD.

8 The data suggest that ED should be regarded as a potential predictor of asymptomatic CAD in patients with uncomplicated type 2 diabetes who are at relatively low risk for CAD.

9 Due to the high ED prevalence in patients with diabetes with silent CAD, the need to perform an exercise ECG before starting to treat the ED would be suggested, particularly in cases where other cardiovascular risk factors are present.

Gazzaruso C, Giordanetti S, De Amici E (2004) Relationship between erectile dysfunction and silent myocardial ischemia in apparently uncomplicated type 2 diabetic patients. *Circulation* **110**: 22–26

'RhoA/Rho-kinase may represent a therapeutic target for the treatment of diabetes-related ED'

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES

RhoA/Rho-kinase suppresses NO synthase in the penis

Readability	✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 The principle mediator of relaxation of the corporal smooth muscle is neuronal- and endothelial-derived nitric oxide (NO). RhoA/Rho-kinase activity has recently been shown to be important in suppression of endothelial NO synthase.

2 The authors hypothesised that in streptozotocin (STZ)-induced diabetic rats, RhoA/Rho-kinase contributes to diabetes-related ED and penile endothelial NO synthase down-regulation.

3 In the corpus cavernosum endothelium, there was co-localisation of endothelial NO synthase and Rho-kinase. In the STZ-diabetic rats there were elevated RhoA/Rho-kinase protein levels and increased MYPT-1 phosphorylation.

4 In the STZ-diabetic rat penis there was a reduction in endothelial NO synthase, reduced cavernosal NO synthase activity and lower cGMP levels.

5 An adeno-associated virus encoding the dominant-negative RhoA mutant was assessed to determine the functional role of RhoA/Rho-kinase in the penis. The effect on erectile function, endothelial NO synthase and RhoA/Rho-kinase in STZ-diabetic rats in vivo was measured.

6 There was a reduction in RhoA/Rho-kinase and MYPT-1 phosphorylation in transfected STZ-rats. There were also corresponding rises in constitutive NO synthase activity, and cavernosal endothelial NO synthase protein and cGMP levels to the same as those found in the control rats.

7 Gene transfer in STZ-diabetic rats led to improved erectile response values similar to control rats.

8 A mechanism of down-regulation of endothelial NO synthase in diabetes is shown by these data. This was mediated by RhoA/Rho-kinase pathway activation.

9 The results of this study imply that RhoA/Rho-kinase inhibition restores erectile function in diabetes by improving endothelial NO synthase protein content and activity.

Bivalacqua TJ, Champion HC, Usta MF, et al (2004) RhoA/Rho-kinase suppresses endothelial nitric oxide synthase in the penis: a mechanism for diabetes-associated erectile dysfunction. *Proceedings of the National Academy of Sciences* **101**: 9121–26

'Hemodialysis patients with diabetes mellitus (DM-HD) are more likely to have ED, and particularly severe forms of ED, than non-DM-HD.'

'. . . adding an ED questionnaire to a screening program may encourage more men to seek treatment, not only for their ED, but also for the underlying disease.'

INTERNATIONAL JOURNAL OF UROLOGY

ED in haemodialysis patients with diabetes

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 In patients with diabetes and those undergoing haemodialysis, ED is common.

2 Here, ED frequency and severity in patients with and without diabetes who were undergoing haemodialysis was examined. The relationship between erectile function and a number of risk factors in the haemodialysis patients was investigated.

3 One-hundred-and-eighty haemodialysis patients (66 with diabetes) had their erectile function evaluated with the use of an abridged version of the IIEF-5 questionnaire.

4 The relationship between ED presence and risk factors was measured using logistic regression analysis.

5 Haemodialysis patients without diabetes had a significantly higher IIEF-5 score than those with diabetes. Severe ED prevalence was 18.4 % vs 42.4 % respectively for those without and those with diabetes.

6 Independent risk factors for ED were diabetes, age and cardiovascular disease. Those for severe ED were age and elevated HbA_{1c} levels.

7 Patients undergoing haemodialysis are more likely to have ED if they also have diabetes. ED or severe ED was associated with elevated HbA_{1c} and diabetes respectively, and ageing was an independent factor.

Miyata Y, Shindo K, Matsuya F, Noguchi M, Nishikido M, Koga S, Kanetake H (2004) Erectile dysfunction in hemodialysis patients with diabetes mellitus: association with age and hemoglobin A1c levels. *International Journal of Urology* **11**: 530–34

INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH

Screening for ED: concept and implementation

Readability	✓ ✓ ✓ ✓
Applicability to practice	✓ ✓ ✓ ✓
WOW! factor	✓ ✓ ✓

1 ED can be a symptom of systemic disease, such as diabetes, and can be a marker of disease progression.

2 This study aimed to cover the concept and implementation of having a questionnaire as part of an ED screening programme.

3 In order to detect early morbidity, the Israeli Defense Force offered a screening programme for servicemen at the staff periodic examination centre.

4 The Sexual Human Inventory for Males (SHIM) questionnaire was given to people undergoing the examination in order to identify those with ED and offer suitable treatments.

5 Medical history was collected using a computerised questionnaire with the SHIM incorporated into it. Details on age, SHIM scores, compliance to reply and accompanying diseases were collected.

6 Of the data collected from 1980 males, 881 (44.5 %) filled in the SHIM questionnaire and 244 (27.7 %) had a score of ≤21.

7 Those with a score of ≤16 had a higher prevalence of diabetes and hypertension than those with a score of ≥22. There was an inverted linear correlation between SHIM score and age ($p<0.0001$).

8 As few men with ED ask for treatment, adding an ED questionnaire to a screening programme may encourage more to seek help for their ED and underlying disease. Better patient cooperation is seen due to the privacy of a periodic examination, making it a good screening platform.

Heruti RJ, Yossef M, Shochat T (2004) Screening for erectile dysfunction as part of periodic examination programs – concept and implementation. *International Journal of Impotence Research* **16**: 341–45

BJU INTERNATIONAL

Aminoguanidine protective effect not time-related

Readability	✓ ✓ ✓
Applicability to practice	✓ ✓
WOW! factor	✓ ✓ ✓ ✓

1 ED development in men with diabetes and accumulation of advanced glycation end products (AGEs) in the penile tissue are closely linked.

2 This study aimed to assess AGE accumulation in the cavernosal tissue of STZ-diabetic rats, and see whether the protective effect of aminoguanidine on erectile function is related to treatment timing.

3 Four groups of rats were included in the study – 1: age-matched controls; 2: STZ-diabetic rats given free water access; 3: STZ-diabetic rats given aminoguanidine 1 g/L per day in drinking water immediately after diabetes induction; 4: STZ-diabetic rats given aminoguanidine a month after diabetes induction.

4 Cavernosal AGE level was assessed as was intracavernosal pressure (measured after cavernosal nerve stimulation) two months after diabetes was induced.

5 Cavernosal AGE levels were significantly higher in groups 2 and 4 than the control group (1), which had similar levels to group 3.

6 Groups 3 and 4, containing diabetic rats treated with aminoguanidine, had normal erectile function compared to group 2 which showed significant impairment.

7 Aminoguanidine appears to have a time-dependent effect on AGE levels – with no change in AGEs, one-month treatment with aminoguanidine, improved erectile function suggesting protective effects on penile vasculature.

Usta MF, Bivalacqua TJ, Koksal IT, Toptas B, Surmen S, Hellstrom WJG (2004) The protective effect of aminoguanidine on erectile function in diabetic rats is not related to the timing of treatment. *BJU International* **94**: 429–32