

Erectile Dysfunction: Recent Trends in Management

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Abstract: Erectile dysfunction (ED) is a widely occurring disorder that affects men of all ages. The prevalence and severity of ED increases with age and results in considerable distress and impact on quality of life. ED often has multiple causes, and diagnostic evaluation should include psychosexual, endocrinological, neurological and vascular factors. Treatment includes oral therapy with sildenafil, tadalafil, apomorphine, phentolamine; intracavernosal and intraurethral alprostadil or papaverine; vacuum erection devices, penile vascular surgery and penile implants. This article presents a brief overview of the diagnosis, treatment options and the upcoming therapies for the management of ED.

Key Words : *Erectile dysfunction; Sildenafil; Tadalafil; Alprostadil.*

Introduction

Erectile dysfunction (ED) can be defined as an inability to sustain or maintain penile erection of sufficient rigidity for satisfactory sexual performance. Penile erection is a complex series of integrated neural and vascular events culminating in the accumulation of blood under pressure in the penis that causes end-organ rigidity. Any insufficiency at any level will result in failure to achieve erection. Thus ED is a multifactorial disease. Its incidence is strongly related to age with a prevalence of 2% at the age of 40 years, rising to 25-30% at the age of 65 years¹. ED can have a strong negative effect on the well being and quality of life and can cause psychological imbalance. Therefore, it is imperative to examine a patient thoroughly (both medically as well as psychologically) to diagnose the problem of ED and treat it accordingly.

Etiology

Psychological : This is the commonest cause of intermittent erectile failure in young and middle aged men. It usually occurs secondary to some organic dysfunction². Clinically higher levels of serum nor-epinephrine have been reported in patients with psychogenic ED as compared to normal controls or patients with vasculogenic ED.

Neurogenic : Any lesion at the level of brain, spinal cord, cavernous and pudendal nerves can cause ED. Parkinson's disease, stroke, tumor and Alzheimer's disease are also often associated with ED. Injuries and disorders at the spinal level (e.g. spina bifida, dislocation, syringomyelia, tumors and multiple sclerosis) may affect the erectile function. Iatrogenic impotence can occur following various surgical procedures like radical prostatectomy, perineal prostatectomy³, abdominal perineal resection and external sphincterotomy⁴.

Endocrinal: Diabetes mellitus (DM) is the commonest endocrinal disorder causing ED. It has been reported that men with diabetes have fewer sleep related erections, less tumescence time, diminished penile rigidity, lower penile blood pressure than age matched non-diabetic men⁵. DM causes ED through its vascular, neurogenic, endothelial and psychogenic complications rather than insulin deficiency per se⁶. Both hyperthyroidism and hypothyroidism⁷,

decreased testosterone concentration⁷ and hyperprolactinemia are associated with diminished libido and ED.

Vasculogenic : Adequate venous occlusion is one of the important prerequisite for erectile process. Incidence and age at the onset of coronary artery disease and ED is said to run parallel⁶. Arterial insufficiency, hypertension, hyperlipidemia, cigarette smoking and DM are the common risk factors for vasculogenic ED. Venocclusive dysfunction can also be due to degenerative changes e.g. Peyronie's disease⁸, old age and traumatic injury to albuginea resulting in inadequate compression of subtunical and emissary veins.

Iatrogenic : They are often the culprits and around 25% of all ED can be attributed to medications⁹. Antiandrogens (cimetidine, spironolactone, ketoconazole, finasteride), antihypertensives (clonidine, methyl dopa, beta-blockers, thiazides), antidepressants (MAO inhibitors, tricyclic antidepressants, barbiturates and benzodiazepines), digoxin, metoclopramide and anabolic steroids are likely to produce ED.

Diagnosis

Careful history and physical examination form the initial step in the diagnosis of ED. Blood levels of glucose, creatinine, lipids, thyroid hormones, testosterone, luteinizing hormone and prolactin need to be ascertained and are the organic causes of ED. Nocturnal penile tumescence (NPT) occurs for a total time averaging around 10 min/night¹⁰ during rapid eye movement (REM) sleep and its measurement is used as a marker of erectile functions of an individual. If history of nocturnal erection is questionable, NPT can be measured in a sleep laboratory or with the use of a strain gauge or snap gauge band. In the strain gauge test, the patient wraps a strip of strain gauge around penis before sleeping. If the ring breaks along the line of perfection, the test is considered positive indicating occurrence of a rigid erection¹¹. However, the validity of the test is questionable in many cases like psychogenic ED where NPT may be absent¹². Therefore, NPT is not indicated for routine use. Another test used is the measurement of penile buckling pressure in which a pressure device is pressed against the glans penis and the pressure required to make the penis buckle is measured in mmHg. Normal rigid penis buckles if pressure is more than 100mmHg. If the penis buckles at pressure less than 60 mmHg, it is considered too soft for vaginal penetration¹³.

Apart from measuring the rigidity, penile blood flow can also be

measured by Doppler technique. This technique is called as Penile/brachial systolic pressure index and in this penile systolic pressure (as determined by Doppler technique) is divided by supine brachial systolic pressure (measured simultaneously). An index of <0.6 suggests vasculogenic impotence. However, this test is also not confirmatory as it evaluates the blood flow through dorsal penile artery which is not involved in the erectile process and not through cavernosal arteries which are actually involved in erection. Thus, when cavernosal arteries are diseased and dorsal artery of penis is normal, the test will fail to detect impotence. Pulsed doppler analysis and high-resolution ultrasonography can also be used in conjunction with intracorporeal injection of alprostadil to assess blood flow in the cavernosal arteries¹⁴. A simple papaverine stimulation test (usually 40mg with or without 2mg of phentolamine to potentiate its effect) distinguishes responders from non-responders and help select candidates for self-injection treatment¹⁵. Color Doppler imaging after inducing maximal intracavernous smooth muscle relaxation with papaverine provides detailed information about penile hemodynamics and is particularly useful in distinguishing arterial insufficiency from venoocclusive dysfunction¹⁶. No single test is confirmatory, therefore clinician needs to correlate clinical findings with laboratory investigations to diagnose ED and its etiology and offer the patient, most suitable treatment option.

Management

Psychosexual counseling : Psychosexual counseling is essential in treating ED as other treatment will fail in patients of primary psychogenic ED. It is aimed at decreasing performance anxiety by increasing the range of sexual activities and this requires close cooperation of the sexual partner. Therefore both the partners should be counseled.

Hormonal therapy : In young hypogonadal men, depot preparations of testosterone should be given every 2-3 weeks. This treatment improves both the libido and the potency. However, there is a risk of benign prostatic hyperplasia and prostate cancer¹⁵. Thus close monitoring of prostate specific antigen (PSA) and urinary flow rate is recommended before and during this treatment.

First Line Drug Therapy :

Sildenafil : It is a potent inhibitor of phosphodiesterase type V (PDE5)- the predominant isoenzyme responsible for degradation of cGMP¹⁷. Since the drug only potentiates the action of cGMP rather than stimulating its production, it acts only in response to sexual stimulation. It is predominantly eliminated by hepatic metabolism (mainly by cytochrome P450 3A4) and converted to an active metabolite S-desmethyl-sildenafil. Half-life of both sildenafil and its metabolite is about 4 hours¹⁸.

Sildenafil (25,50 and 100mg) has been evaluated clinically in various trials. A review of these studies indicates that it is effective in a broad range of ED patients regardless of etiology, severity and age. In a randomized, double blind, placebo controlled study, in patients with ED due to diabetes mellitus (n=268), 57% of patients receiving sildenafil reported improved erections versus 10% on placebo (P<0.0001)¹⁹. Report of another randomized, double blind, placebo controlled, crossover, flexible-dose (up to 100mg) study²⁰ in patients with ED resulting from spinal cord injury have shown highly statistically significant score in sildenafil

group versus placebo. Improvement in erectile function was seen in 16 of 25 (64%) patients with no residual erectile function and 111 of 143 (78%) patients with erectile function (P<0.0001) after sildenafil (doses ranging from 25-100mg). Commonly reported adverse effects in trial 21 were headaches (16%), flushing (10%), dyspepsia (7%), nasal congestion (4%), urinary tract infection, diarrhea (all 3%), dizziness (2%) and abnormal vision. Till November 1998²², more than 6 million sildenafil prescriptions were dispensed and the FDA had reported 130 deaths in patients who were prescribed the drug in US. In 48 patients, causes of death were unknown, 41 patients had a known or suspected myocardial infarction, 27 had cardiac arrest, 3 had coronary artery disease. The interval between ingestion of sildenafil to death was between 4-5 hours (34%) patients, and time interval were unknown for 48% patients. Cardiovascular risk factors existed in 70% of patients²². It is contraindicated in patients taking nitrates or nitric oxide donors because of potential danger of hypotensive episodes and ischemia during coitus¹⁸. The drug should also be avoided in those for whom sexual activity carries a major cardiovascular risk. It should be used with caution or better avoided in patients with unstable angina, heart disease, with recent history (<6 months) of heart attack activity carries a major cardiovascular risk. It should be used with caution or better avoided in patients with unstable angina, heart disease, with recent history (<6 months) of heart attack, stroke or life threatening arrhythmia, hypotension or uncontrolled hypertension and retinitis pigmentosa²³.

Tadalafil : Another PDE5 inhibitor tadalafil, had been shown to be about 20,000 to 44,000 and 800 times more selective inhibitor of PDE3 and PDE5 versus PDE5 respectively. Thus, the PDE5:PDE6 selectivity ratio of tadalafil more than 2 orders of magnitude higher than that of sildenafil. Further, the maximum serum tadalafil concentration is reached in 2 hours, but the geometric mean half-life of tadalafil is 17.5 hours²⁴. This pharmacological profile is consistent with a broader clinical period of responsiveness. This long half-life (>17h), with a comfortably long window of opportunity, releases couples from the need to plan sexual activities and therefore provides the highest amount of spontaneity for sexual activities. Neither drug-related serious cardiovascular adverse events nor color vision disturbances were encountered in the European daily-dosing trial and placebo-controlled, fixed-dose (10-and 20-mg) trial in diabetic patients²⁵ with this drug.

Vardenafil : It is another selective, orally active PDE5 inhibitor with a mean tmax of 34 minutes and has already undergone phase 2 clinical trials. It has been shown to be effective in ED regardless of age, etiology, or severity of ED in a phase 3 trial. In these patients on the 20-mg dose, adverse events > 2% included flushing (10-11%), headache (15%) and dyspepsia (7%), vision disturbances (4%)²⁶.

Second line drug therapy

Alprostadil : Intra-cavernosal injection of PGE-1 causes smooth muscle relaxation and vasodilatation leading to erection. It is metabolized by enzyme prostaglandin 15-OH dehydrogenase, which is active in corpus cavernosum²⁷. After IC injection, 96% of PGE-1 is locally metabolized within 1 hour and no change in peripheral blood levels has been observed²⁸. Usually a good response is seen with a dose of 20µgm alprostadil. In one large

trial²⁹ (n=187) of ED patients, use of PGE-1 was associated with good erectile response and sexual satisfaction in 91% of recipients. In another open flexible dose study³⁰ (n=683) ED patients were given PGE-1. Out of those receiving PGE-1, 87% of patients reported a satisfactory sexual performance. In another trial,³¹ comparing papaverine and phentolamine mixture (7.5-60mg papaverine + 0.25-2 ng phentolamine) with alprostadil 10-20mcg), adequate erection was seen in 67.1% of 51 patients given papaverine + phentolamine mixture and in 79.1% of 76 patients given alprostadil side effects reported were pain at injection site (16.1%), ecchymosis and hematoma (1.5%), priapism (1.3%). The incidence to priapism was less in comparison to papaverine.

Alprostadil can also be given trans-urethraly and the technique is called as medicated Urethral System for Erection (MUSE). It involves the placement of PGE-1 pellet into the urethra by an applicator after the man has passed urine. Within 10 min, up to 80% of PGE-1 is absorbed by the urethral mucosa, leading to a significant increase in cavernosal artery blood flow. The effectiveness of MUSE was studied in a double blind placebo controlled prospective study³² where in 1511 men aged between 27 and 88 years with ED of varying etiology were enrolled. In clinical testing with MUSE, an erection adequate for intercourse was attained in 65.9% of administration. The MUSE was found to be effective regardless of age of the patient and etiology of ED. The most common side effect reported was penile pain.

In a direct comparative trial of IU and IC alprostadil, Porst showed that IC alprostadil had clinical advantages over the IU administration route. The percentage of subjects showing completely rigid erections with maximal cavernous smooth-muscle relaxation was 48 and 10% respectively. Moreover the rate of penile pain or burning was nearly 3 times higher with IU than IC alprostadil and circulatory adverse events (e.g., dizziness, sweating, hypotension) were reported only in the IU alprostadil group³³.

Third Line drug therapy :

Apomorphine : It has been found to work effectively in patients of ED with a wide range of etiology, severity and co-morbidity. It is well tolerated if given by sublingual (SL) route. In a cross-over study comparing apomorphine (3mg SL) with placebo, it produced a rapid response with 71% of erections occurring within 20min³⁴. Three mg apomorphine SL was significantly more effective than placebo ($p < 0.001$) for the percentage of attempts resulting in erections firm enough for intercourse and resulting in intercourse, as assessed by both patient and partner. Median time to erection was 18.8 min. About 5% of patients treated with this medication at a dose of 2mg or 3mg report nausea, and the recommended dose regimen of apomorphine SL can cause a transient vasovagal syndrome (incidence $< 0.2\%$) with fainting/syncope³⁴.

Phentolamine : It is non-specific alpha-receptor antagonist that has been shown to have erectogenic activity. In one study erectile response rates of 30-40% were reported with buccal administration of phentolamine compared with 15-20% with placebo³⁵. Lawless and Cree³⁶ reviewed the clinical efficacy of phentolamine in ED. They concluded that patients with non-organic dysfunction received the greatest effect of phentolamine, with that effect possibly being dose dependent as well. Oral route provided a much better response in comparison to buccal phentolamine of lower dosages.

Yohimbine : It is an orally administered iminoalkaloid alkaloid agent with peripheral alpha-2 adrenergic receptor blocker activity and central noradrenergic agonist activity. In a double-blind partial cross-over study³⁷, 82 patients with ED were given yohimbine. After 1 month of treatment, 14% experienced full and sustained erection, 20% reported partial response and 65% reported no improvement. The 34% response was encouraging because there was a high incidence of diabetes and vascular pathological condition in the population enrolled in the study. It appears that yohimbine may be useful in younger patients, with ED of shorter duration (< 2 years), independent of the degree of severity. The recommended dose is 27 mg given 30 min prior to sexual activity³⁸. The most common adverse effects with yohimbine include anxiety, increased urinary frequency, tachycardia, and increased arterial pressure^{38,39}. In a trial by Rowland et al,⁴⁰ the more common adverse effects in the yohimbine group included disturbed sleep, mild diarrhea, lack of energy, and, surprisingly, lower sexual desire. Susset et al³⁸ assessed 82 patients with ED of mixed causes to study which patients might benefit most from yohimbine treatment. Patients received either placebo or 5.4mg of yohimbine four times daily. The dose of yohimbine was gradually increased to 10.8 mg four times daily throughout the 4-week study. Positive results were found in 34 percent of patients taking yohimbine. The authors found that patients who had mild dysfunction, short duration of erectile dysfunction (less than 2 years), lower levels of arterial insufficiency, and high-normal testosterone levels responded significantly better. Thus, yohimbine is not a very effective agent for organic ED patients and should be preferably used for psychogenic or non-organic ED. However, Hatzichristou and Pescatori⁴¹ who reviewed treatment of erectile dysfunction concluded that studies demonstrating significant efficacy of Yohimbine suffer from methodological flaws and therefore do not have a significant advantage even in psychogenic ED.

Moxisylyte hydrochloride : It is alpha-1 selective adrenergic blocker. In a placebo controlled study⁴² in patients of neurogenic ED, an IC injection of 10-30 mg of moxisylyte resulted in a complete erection in 58% patients compared with 0% in placebo group. A study showed that in comparison to PGE-1, the efficacy of moxisylyte is quite low. While moxisylyte resulted in successful sexual intercourse in 46% of patients, 81% patients using PGE-1 reported sexual intercourse. Thus moxisylyte is only of value in patients who cannot tolerate PGE-1 induced pain, fibrosis of priapism.

Pentoxifylline : Patients taking this drug for treatment of claudication of lower limbs reported improved sexual function while on this medication⁴³. Therefore, pentoxifylline 1.2 g in three divided doses orally for 8 weeks was assessed in patients with ED due to borderline arterial insufficiency (n=36) in ED patients. Therapy was found to increase peak systolic velocities (PSVs) at the end of the treatment. The mean change in PSV achieved by pentoxifylline treatment (6.25 cm/s) was significantly higher than that achieved by placebo (0.38 cm/s). Seven patients had a positive response (successful coitus achieved after treatment with pentoxifylline). No serious side effects were reported⁴⁴.

Serotonergic drugs : In experimental studies, serotonergic system had exhibited an inhibitory effect on sexual behavior and therefore agents with anti-serotonergic properties have been tried in ED⁴⁵. In a double blind, randomized, placebo controlled trial⁴⁶, trazodone,

ketanserin, and mianserin given orally were investigated in terms of effectiveness in ED. Patients aged 23-68 years believed to have ED of non-organic etiology were selected on the basis of their response to intra-cavernosal papaverine. The patients were randomized into 4 groups, 25 in each group received 50mg trazodone tid or 20 mg ketanserin bid or 10mg mianserin tid or placebo for 30 days. The positive response in trazodone group was higher (65.2%) as compared to ketanserin (19%), mianserin (31.6%) and placebo (13%). In trazodone group, one patient reported priapism, one experienced severe sedation, while two had xerostomia and one blurred vision. Currently these drugs have no role in the management of ED because of their limited efficacy, greater side effects and availability of safer agents.

Papaverine : Papaverine inhibits phosphodiesterase enzyme leading to an increased cAMP and cGMP in penile erectile tissue. It also blocks voltage dependent calcium channels, decrease in calcium influx and impairment to calcium activated potassium and chloride currents⁴⁷. All these mechanisms lead to relaxation of cavernous smooth muscle cells and penile vessels. Papaverine, metabolized in liver has a half-life of 1-2 hours. It has been shown to be effective in both psychogenic and neurogenic ED. The advantages are its low cost and stability at room temperature. Important side effects are priapism (up to 35%), corporal fibrosis (up to 33%) and elevation of liver enzymes.

Therapies under development

Vasoactive intestinal polypeptide (VIP): VIP, originally isolated from small intestine, is a potent smooth muscle relaxant. It is proposed that VIP may be a neurotransmitter for penile erection. Studies showed that IC injection of VIP only leads to tumescence and does not produce rigid erection⁴⁸. Therefore, it was combined with other drugs like phentolamine and was found to be very effective⁴⁹. In a study of 52 men with ED of mixed etiology who exhibited full response to papaverine, IC injection of 30µg + 0.5-2 mg phentolamine led to a functionally rigid erection in 100% cases. Even after 6 months of follow up, there were no complaints of pain, corporeal fibrosis or priapism. The combination of VIP and phentolamine is efficacious and a safe alternative for patients who suffer from PGE-1 induced pain.

Calcitonin gene related peptide (cGRP): It is a potent vasodilator and has been shown to relax strips of cavernosal smooth muscles *in vitro*. Immunohistochemical techniques have localized cGRP in cavernosal nerves, within the walls of cavernous arteries and in cavernous smooth muscles⁵⁰. Moreover, cGRP injection induced an increase in the penile arterial inflow, cavernous smooth muscle relaxation and cavernous outflow occlusion. Dose-related increase in penile blood flow. Clinically the combination of cGRP and alprostadil has been reported to be effective in 56% of patients in whom other drugs had failed⁵¹. Systemic side effects included facial flushing and hypotension. cGRP is contraindicated in sickle cell anemia, severe psychiatric disorders like schizophrenia and severe venous incompetence.

Transcutaneous nitroglycerin : Using ultrasound, Heaton et al⁵² have showed a 46% increase in penile arterial diameter 10min after applying glyceryl trinitrate locally to the shaft of penis. In a randomized placebo controlled study⁵³ of transcutaneous nitroglycerin therapy in 26 patients with ED, satisfactory sexual function was reported in 46% of patients and some erectile

improvement in a further 35% while placebo showed an improvement in only 1 patient. Headache was the most common side effect noted and 15% of patients were excluded from the trial because of persistent headache.

Topical Creams

Triple Vasodilator Combination : A topical cream containing 3 vasodilators (3% aminophylline 0.25% isosorbide dinitrate and 0.05% codergocrine mesylate) was evaluated in a double blind placebo controlled cross over study⁵⁴ in 36 men with ED of mixed etiology. Results showed that 58% of men using cream attained an erection adequate for sexual intercourse compared to 8% using the placebo. The cream was particularly effective in men with psychogenic ED. With duplex scanning, a significant increase in penile arterial flow was observed on application of the cream as compared to the placebo.

Mechanical Intervention

Vacuum erection devices (VEDs): These devices use a vacuum pump to increase blood flow to the corpora cavernosa to induce an erection. They also have a constrictor ring to retain blood within the corpora and thus maintain the erection. VEDs are a safe, reasonably affordable and effective and can be offered as a noninvasive first-line therapy, particularly in patients for whom oral drug therapy is contraindicated. However VEDs are cumbersome to use and lack spontaneity. As this technique is based on the retention of static blood within the corpora, it can cause penile coldness. Further skin bruising may also occur in some patients.

Penile vascular surgery : It should only be used in young impotent patients, with pure arteriogenic impotence secondary to blunt pelvic or perineal trauma and with no evidence of generalized atherosclerosis of other vascular risk factors.

Penile Implants : The most invasive and usually the last resort in the treatment of ED is insertion of a penile implant. This procedure is usually performed when all other methods or drugs fail. Penile implants are more reliable but have the disadvantage of potential life changing surgery. It is important to inform the patient that penile implants surgery is irreversible.

Conclusion :

With the increase in geriatric population and diabetes, the number of patients with ED is bound to increase in near future. Therefore physicians have to be updated about the therapeutic options available. It is mandatory to obtain a detailed medical history with a thorough medical examination before diagnosing ED. Apart from PDE5 inhibitors and others under development (e.g., vardenafil), treatment with the dopamine agonist apomorphine, local therapies with vasoactive agents (e.g., alprostadil) either alone or in combination with PDE5 inhibitors, and penile implants represent sound second-and third-line clinical options. Intra-cavernosal therapy suffers from a high rate of discontinuation because of pain at the site of injection, ecchymosis and priapism. Sildenafil has come out as a boon in patients with ED. But it should be cautiously prescribed in patients with cardiovascular risk. Along with drugs psychotherapy plays a major role in treating ED. Lawless and Cree, 1998 reviewed the data of various treatment modalities in ED on the basis of subjective benefit to the patient and safety, tolerability, efficacy, and cost-effectiveness of

therapy. They concluded that yohimbine is effective in 60 to 80% of patients of psychogenic ED and not effective in organic ED. Sildenafil is effective in 56 to 85% of ED of mixed etiology and >80% effective in patients with non-organic ED. Phentolamine was 30 to 40% effective in combined populations and 70% effective in purely non-organic ED (Lawless and Cree, 1998). In comparison to these oral therapies, vacuum constriction devices have a success rate of >80% for achieving an erection sufficient for intercourse, and penile injection therapy has a success rate >89% for all causes of dysfunction. Thus in comparison with these therapies, the efficacy of oral medications was quite less. However, drugs are still preferred over the non-drug modalities as they are non-invasive and allow more spontaneity.

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ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

The need for uniform ethical guidelines for research on human subjects is universally recognised. It has acquired a new sense of urgency as the critical issues in the area of biogenetic research involving human subjects have become acute. Apart from the mandatory *clinical trails on new drugs, a number of diagnostic procedures, therapeutic interventions and prevention measures* including the use of vaccines, are being introduced which involve human subjects. Further the advent of *new medical devices and radio-active materials* and therapeutic benefits of *recombinant DNA products* have added a new dimension to the ethical issues that need to be considered before evaluating these for their efficacy, utility and safety.

Any research using the human beings as subjects shall bear in

mind the following principles of : i) **essentiality**, (ii) **voluntariness**, **informed consent**, (iii) **non exploitation**, (iv) **privacy and confidentiality**, (v) **precaution and risk minimisation**, (vi) **professional competence**, (vii) **accountability & transparency**, (viii) **maximisation of public interest and distributive justice** (ix) **institutional arrangements** (x) **public domain** (xi) **totality of responsibility** and (xii) **compliance**.

Recent advances in the field of **Assisted Reproductive technologies, organ transplantation, Human genome analysis, and gene therapy** promise unquestionable benefits to mankind. At the same time, they raise many questions of law and ethics, stimulating public interest and concern.

(Source : ICMR Publication 2000)

Literature Review

Compiled by Dr. PD Gulati

Decline of renal function is associated with proteinuria and systolic blood pressure in the morning in diabetic nephropathy. Suzuki H, Kanno Y, Nakamoto H, Okada H, Sugahara S. *Clin Exp Hypertens.* 2005 27(2-3):129-38.

The aim of this study was to investigate a significance of increased proteinuria in the morning and the effects of antihypertensive treatment on proteinuria and arterial blood pressure in the progression of chronic renal insufficiency in type 2 diabetic patients with hypertension and nephropathy. In three 24-hr urine samples and blood pressure monitoring, separated into a night- and daytime and spot urine in the morning, variation in protein-creatinine ratio (g/g) and blood pressure were assessed in 24 (58 ± 3years old; M/F: 17/7) diabetic patients with hypertension and nephropathy. Furthermore, the effects of antihypertensive therapy of combinations of angiotensin converting enzyme (ACE) inhibitor, calcium antagonists, diuretics, and alpha blocker were evaluated in 3 years. Home blood pressure measurement was carried out every month and 24-hr urine was collected every 2 months. The baseline urine excretion of protein-creatinine ratio and blood pressure were (1.22 ± 0.13 g/g creatinine: 154/96 ± 6/5 mmHg) in daytime and (1.39 ± 0.13: 168/88 ± 15/7) in the morning. At the end of the study, significant associations among a decline of 24-hr creatinine clearance and both of the urine excretion of protein-creatinine ratio (r=0.47, p<.01) and the levels of systolic blood pressure (r=0.46, P<.01) and between the levels of systolic blood pressure and the urine excretion of protein-creatinine ratio in the morning (r=0.57, p<.001) were demonstrated. However, there were no significant associations among other variables. Analysis of patients who had systolic blood pressure in the morning less than 140 mmHg revealed that 65% of these patients received doxazosin-averaged

doses of 4.8 ± 1.5mg daily. The levels of both blood pressure and proteinuria-creatinine ratio in the morning mainly associate with progression of renal function in diabetic patients with hypertension and nephropathy.

Why Are Indian More Prone to Diabetes. V. Mohan. *JAPI.* 2003; 780-781.

Diabetes, a global public health problem, is now emerging as a pandemic and by the year 2025, three-quarters of the world's 300 million adults with diabetes will be in non-industrialized countries and almost a third in India and China alone. There is evidence from several studies that the prevalence of Type 2 diabetes is increasing in migrant Indians. Today, the prevalence of diabetes in the urban metros of India is approaching the figures reported in the affluent migrant Indians. Environmental and lifestyle changes resulting from industrialization and migration to urban environment from rural settings may be responsible to a large extent, for this epidemic of Type 2 diabetes in Indians. Obesity, especially central obesity and increased visceral fat due to physical inactivity, and consumption of a high-calorie/high-fat and high sugar diets are major contributing factors. There is also strong evidence that Indians have a greater degree of insulin resistance and a stronger genetic predisposition to diabetes. As several of the factors associated with diabetes are potentially modifiable, the epidemic of diabetes can be curbed if proper measures are taken to increase physical activity and reduce obesity rates in adults, and most importantly, in children. In addition, strategies to achieve healthy fetal and infant growth and encouraging the use of traditional diets rich in fibre are also important steps. Such interventions should be attempted in those who are genetically predisposed to diabetes in order to tackle explosion of, and thereby reduce the burden due to, diabetes within the Indian subcontinent.