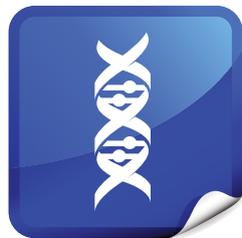


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## Managing Diabetes Challenges & Opportunities

INDIAN EDITION

### FEATURED ARTICLE

Diabetes in India:  
The Current Scenario

### EDITOR'S CHOICE

Patients at Center Stage: Diabetes  
Control through Self-management

### INTERVIEW

Clinical Perspectives on  
Diabetic Retinopathy

### REVIEW ARTICLE

Type 2 Diabetes in India:  
An Epidemiological Overview



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## INTERVIEW

## Clinical Perspectives on Diabetic Retinopathy

**Dr Gregory Jackson**

Director of Clinical Research and  
Associate Professor of  
Ophthalmology,  
Penn State College of Medicine,  
Hershey, Pennsylvania

Dr Jackson received his PhD in Psychology in 1998, and he is an expert in psychophysics and electrophysiology. For the past 12 years, Dr. Jackson has studied aging-related vision problems, age-related macular degeneration, and diabetic retinopathy. He has developed a novel diagnostic test, the AdaptDx, for the detection of age-related macular degeneration.

**Q: Could you elaborate on the retinal and functional markers of diabetic retinopathy (DR)?**

**A:** Almost every aspect of vision is negatively affected by diabetes and diabetic retinopathy. Patients experience difficulty with vision, before they lose the ability to read small letters on an eye chart. Patients may experience difficulty with their night vision, color vision, or peripheral vision, but still have normal visual acuity. Some patients may exhibit large deficits in their visual field and only have a few microaneurysms visible on retinal examination.

**Q: What is the significance of early detection of DR? Does keeping the blood sugar level under check prevent the disease development or progression?**

**A:** Tight control of blood sugar decreases the risk of DR and slows its progression. The mechanisms responsible for this positive effect are incompletely understood.

Early detection of DR is important and screening for this eye disease should be as widely practiced as screening for glaucoma. Many patients with type 2 diabetes first learn that they have diabetes based upon the finding of DR at an eye examination. Early detection of DR provides an opportunity for patient education about the management of the disease. Modifying the patient's blood sugar control may be one positive approach. Impressing upon the patient, the need for regular eye examinations, will also help prevent blindness.

**Q: What is the key advantage of anti-vascular endothelial growth factor (VEGF) therapy in contrast to other conventional strategies?**

**A:** Anti-VEGF therapy may preserve night vision and peripheral vision, which are sacrificed by traditional laser surgery. Current therapies and anti-VEGF may preserve visual acuity, but vision is a rich sensory experience, and to improve patient outcomes earlier treatment is much required.

**Q: In your opinion, what is the future of ranibizumab in the treatment of DR?**

**A:** My hope is that ranibizumab or similar therapies should be an effective replacement to laser treatment. Although laser therapy is effective, it is also destructive to the retina, and causes night vision and peripheral vision deficits. It would be a major advance in the treatment of patients with DR if ranibizumab is found to be equally effective as laser treatment and less damaging to the retina.

**Q: When is optical coherence tomography (OCT) indicated in patients with DR?**

**A:** My scientific view is that OCT measurements should be taken more often

in patients with DR. In our studies we find many cases of subclinical diabetic macular edema (DME) using the OCT. I think it is important for the clinician to have this information so that follow-up examinations can be scheduled appropriately, and the patient can be educated about possible visual symptoms they may experience. In the future, with improved treatments for DME, OCT will be an important tool in the management of DME.

**Q: Do you support the use of color vision testing alone or in combination with other techniques for screening DR?**

**A:** Color vision is a relatively inexpensive method to screen for DR. However, color vision is confounded by age-related changes in the lens of the eye and most notably cataract formation. There are inexpensive methods to measure contrast sensitivity that would perform equally well. In addition, there are rapid visual field tests that are highly sensitive to DR, albeit at a higher equipment cost.

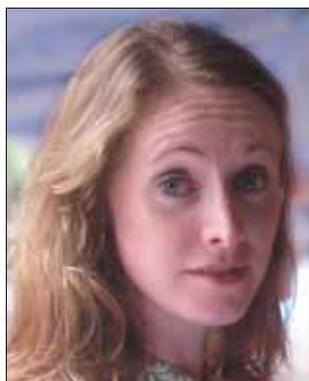
**Q: Are there any particular areas you would like to see new research in the management of DR?**

**A:** A better understanding of the relationship between blood sugar control and the incidence and progression of DR is required. It appears that inconsistent regulation or changes in control may take months to impact retinal health. Because there is an apparent lag between changes in blood sugar control and retinal health, long-term natural history studies will be required to better understand the relationship between them.

**Q: What are your current research activities in the field of DR?**

**A:** New clinical trial endpoints are needed to evaluate novel therapies aimed at early disease management before severe vision loss occurs. My current research is focused on developing better clinical trial endpoints for diabetic retinopathy studies, and better screening methods for early detection in optometry or endocrinologists offices. ■

## Patients at Center Stage: Diabetes Control through Self-management



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*Summary: Most activities involved in managing diabetes take place outside the clinic. As such, patients are ultimately responsible for their glycemic control. For this, patients need the knowledge, skill, and confidence to make healthy decisions. Healthcare providers play a pivotal role in supporting patients become active, successful managers of this disorder.*

### Notes from Dr SM

When I first started practicing, I had a different approach to care. I had learned much in school about diabetes; I felt that if I told patients all the things and what to do, I would control their diabetes; but, I was constantly frustrated with non-compliant patients.

A colleague asked me whether I considered that my patients only saw me four times a year, and that for 361 days, they managed their diabetes; I had not. She challenged me to learn more about how patients manage on their own and to incorporate this into my practice.

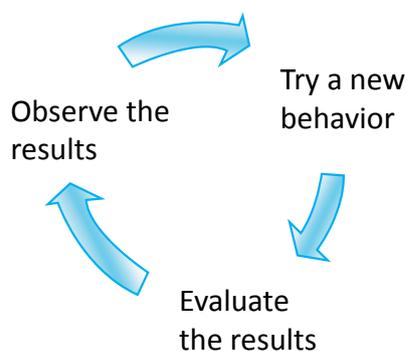
At first, I did not like the idea, but needing to try something new, I tested self-management as a tool to help my patients control their diabetes. I began to see what patients did between clinic visits as potentially helpful, rather than harmful, to glycemic control.

I have seen a huge improvement in my patients, in HbA1c levels and in satisfaction. My role isn't to manage my patients' illnesses, but to help them manage. In my clinic, their life is in my hands. Outside of the clinic, everything is in their hands.

### A. Background and Definition

Individuals make the majority of decisions and actions that determine glycemic control.<sup>1, 2</sup> Achieving an optimal glycemic control in real-world settings has proved difficult, but possible.<sup>4</sup> The central premise of self-management is that diabetic patients, not healthcare providers, manage their disorder on a daily basis. Individuals cope with illness through a collection of strategies, called 'self-management'.<sup>1, 5</sup>

Patients often choose from recommendations - those that fit easily into their lifestyle.<sup>6</sup> Individuals sample coping strategies: (1) *trying* different behaviors, (2) *observing* results, and (3) *evaluating* whether the new behavior is 'worth it,' based on symptom alleviation or functional capacity (Figure 1).<sup>1</sup> For example, they may reduce tension, but not make changes in diet or smoking behavior. By actively working with patients, healthcare providers can guide behavior to align more closely with clinical recommendations.



**Figure 1.** Individuals use the decision making cycle to select coping strategies they determine to be beneficial.

As a process, self-management is not new. Every day, people decide on what to eat, whether to smoke, and whether to exercise.<sup>7</sup> What is new is, focusing on how they make these decisions. In the past, patients have not revealed their management strategies to healthcare providers for fear of being criticized or taking up more of the provider's time. We think this should change. Healthcare providers can help patients understand that changes in observations, feelings, and subsequent evaluations provide opportunities to become better self managers.

This review does not reflect on the lack of literature/reviews on self-management<sup>8,9</sup> rather, we hope to bring self-management to a new audience: those who will read this in the spirit of continuous professional development.

## B. Self-management Tasks

### Notes from Dr SM

I used to think if I told people their HbA1c values and to exercise and eat properly, they would change; but, patients do not think of their problems in terms of numbers. Patients are concerned about how they feel.

Self-management has three overlapping sites for action.<sup>10</sup>

- 1. Medical management** includes adhering to specific behaviors and taking medications, as prescribed.
- 2. Role management** involves learning to participate in one's 'normal' life in spite of diabetes-related restrictions, such as new limits on time or physical functionality.<sup>9</sup>
- 3. Emotional management** involves recognizing that it is normal to feel frustrated or depressed about diabetes, and then to cope with these emotions.

Both, role and emotional management are often overlooked.<sup>8</sup> To refocus, ask the patient what makes

'life worth living', and help the patient discover ways to achieve these things with diabetes.<sup>11,12</sup>

## C. Complete, Personal Understanding Of Diabetes

Patients need to know what to do and why they are doing it. How an individual manages illness is a function of how she/he interprets it, reflecting past illness experiences, social norms, and information from healthcare providers.<sup>13</sup> Patients need a practical understanding that unites with the following five elements of disease information.<sup>14,15</sup>

- 1. Identity:** label for illness and associated symptoms
- 2. Cause:** what led to the illness
- 3. Consequences:** pathophysiological and social effects, short and long term
- 4. Course or timeline:** expected duration; timings and mode of symptom onset
- 5. Treatment:** how to manage illness and symptoms<sup>16</sup>

**Identity:** Patients need to associate symptoms they will experience, as well as lack of symptoms, with high blood sugar.

**Cause:** While patients should receive a complete explanation of causal factors, emphasizing on less changeable elements, such as family history, and physical surroundings, provides less motivation to self manage.

Many people recognize that eating sweets increases blood sugar. A more thoughtful explanation is needed to help patients choose among the wide variety of foods ('traditional' and 'western') that break down into sugars.

**Consequences:** Once people learn that diabetes involves blood sugar, it is easier to explain how every body part can be affected. Patients should have an experiential account of how consequences might feel, such as hypoglycemic shock. A clear explanation of symptoms and their causes should be given to the patients.

**Course or timeline:** Patients must understand that diabetes is permanent, even when symptoms diminish or sugar is controlled. Patients should know which symptoms denote insufficient control, in order to take correct and timely action.

**Treatment:** Once the disease process and complications are understood, management activities make more sense. In prescribing dietary changes, it is important that patients do not become afraid of all food choices, or feel frustrated and overwhelmed, ignore all advice to change.

## D. Collaborative Goals and Action Planning

### Notes from Dr SM

At first, my patients were taken aback. They thought that quickly diagnosing a problem and authoritatively suggesting a solution made a good physician. But, I told them that my solutions don't help if they don't follow them, and their HbA1c numbers told me that they weren't. Even if I generate an accurate solution, it might not be the right solution for each patient.

Before, I never realized that telling patients to 'exercise more' was overwhelming. Most of them didn't know where to begin, so they just didn't do anything.

Patients and healthcare providers both strive to control diabetes. Healthcare providers monitor this through biologic indicators, while patients consider experiences, feelings, and disruptions in their 'normal' lives.<sup>18</sup> These differences obstruct communication and behavior change. Collaborative goal setting is essential for self-management and improved clinical outcomes.<sup>2,10</sup>

Patients and healthcare providers should together explicitly develop self-management goals not tied to biochemical indicators. Explicit means going beyond modifying 'lifestyle' or 'physical activity'; these terms hide the complexities of the individual steps involved. Goals might include walking 5 kilometers without feeling short of breath and maintaining a waist circumference of 80 centimeters or less (women) or 90 centimeters or less (men).<sup>18</sup>

To collaborate, the healthcare provider must allow for open and honest communication. Ask "What is hard for you?"<sup>2,5</sup> Although patients may be used to and like healthcare providers to give instructions, this may not result in glycemic control. Patients must learn how to communicate with their healthcare provider and vice versa.<sup>8</sup>

After establishing goals, patients and healthcare providers should develop an action plan to break down the process of reaching a goal into small, realistic, foundational steps to be undertaken during a one- to two-week span. An action plan list should be developed

on what the patient wants to do.<sup>5</sup> It specifies the days, time, location, amount and duration of each planned behavior. For example, an action item early in the process of walking five kilometers might include walking for 10 minutes before breakfast on four days in a week. The patient might decide to walk on a familiar road, aiming to walk fast enough to feel his/her heart beat. The patient should be fairly confident that the plan can be accomplished.<sup>8</sup> A target set slightly higher than the patient's proposal will challenge patients, making them more likely to succeed. Physicians can also ask the patient to set a goal and then raise it slightly.<sup>19</sup>

By focusing on specific behaviors and outcomes, patients attribute their success to personal effort. When a patient feels that he/she can control diabetes, they will more likely try to do so. Also, patients can evaluate behavioral goals daily, adjusting for slips and changing circumstances. Daily circumstances make patients deviate from clinically recommended strategies, even knowledgeable and motivated to manage diabetes.<sup>9</sup> Too often, healthcare providers address poor control with more facts rather than appropriate applicable tips.

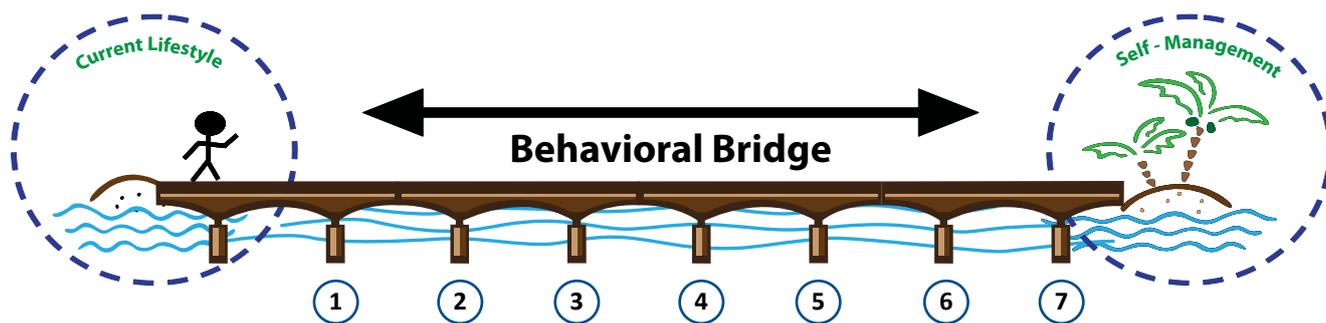
Patients and healthcare providers should explicitly discuss experienced or anticipated barriers to management, such as traveling or financial hardship.<sup>21</sup> Problem solving includes

1. defining the problem
2. generating possible actions to solve the problem
3. implementing a solution
4. evaluating the results<sup>22</sup>

Problem solving also includes learning to interpret and tailor information from a variety of sources to their own situation.<sup>8,23</sup>

## E. Influences

Individuals do not manage their health in a vacuum, or even in a clinic. Outside influences make self-management easier or harder. The Figure 2 depicts these influences as a series of supports of a bridge leading from an individual's current behavior to a lifestyle fully integrating self-management.<sup>1,26</sup> We do not mean that they support different pieces of the journey in a linear fashion, but rather that all of these factors can support the process of moving from one's current life pattern to one in which self-management is integrated.



- |                         |                                 |  |
|-------------------------|---------------------------------|--|
| 1. Family involvement   | 4. Living conditions            | 7. Conducive environment health & policy |
| 2. Social relationships | 5. Work / school support        |  |
| 3. Clinical expertise   | 6. Community awareness & action |  |

**Figure 2.** Each influential group supports the patient in a unique way and can either be a potential agonist or a potential antagonist to the patient successfully managing his condition. As the patient travels on his/her management journey, from an unhealthy life pattern to a healthy one, he/she needs some of these influential groups to support the management efforts. If the influence groups are absent, the patient does not have a bridge to his final destination: a self-managing lifestyle.

**Summary Tips to Help Patients Become Better Self-Managers**

**Notes from Dr SM**

Through my practice, I have learned the benefit of self-management. I no longer feel like I am battling with my patients to encourage them to adopt healthier behaviors. Also, my patients have lower HbA1c levels, fewer emergency clinic visits and higher quality of life. Here are some tips I have learnt through my practice (Figure 3):

1. Acknowledge that the patient is facing an illness that requires difficult behavior changes.<sup>28</sup> Legitimize the seriousness of their disorder.
2. Help the patient gain a coherent understanding of diabetes, explicitly linking its course and consequences with self-management actions.
3. Ask about their biggest concerns in life, even if not related to diabetes. Ask how these concerns and values affect their diabetes.
4. Ask about the most significant change in their life since their last visit. Discuss possible ways for managing diabetes in light of these changes.<sup>29</sup>
5. Remind the patient that diabetes engenders many emotions and guide them towards stress and depression management, as appropriate.
6. Discuss what a patient misses about his/her old life and brainstorm ways to still participate in the things they like.
7. Ask what makes it difficult to manage their diabetes. Brainstorm ways to overcome these obstacles.
8. Help the patient articulate challenging but obtainable goals, and monitor progress. Point out small successes, and use missteps as a chance for brainstorming.
9. Create problem scenarios and have the patient talk through what they would do. This will help patients prepare for obstacles and reveal how much they understand their condition and the needed changes.
10. When asking the patient to make a change or try a new skill, use small steps. Let the patient demonstrate mastery of each until they confidently engage in the whole action.<sup>31</sup>
11. Connect the patient with peer support.
12. Discuss information patients receive on health from various sources; help them understand what is a true claim.

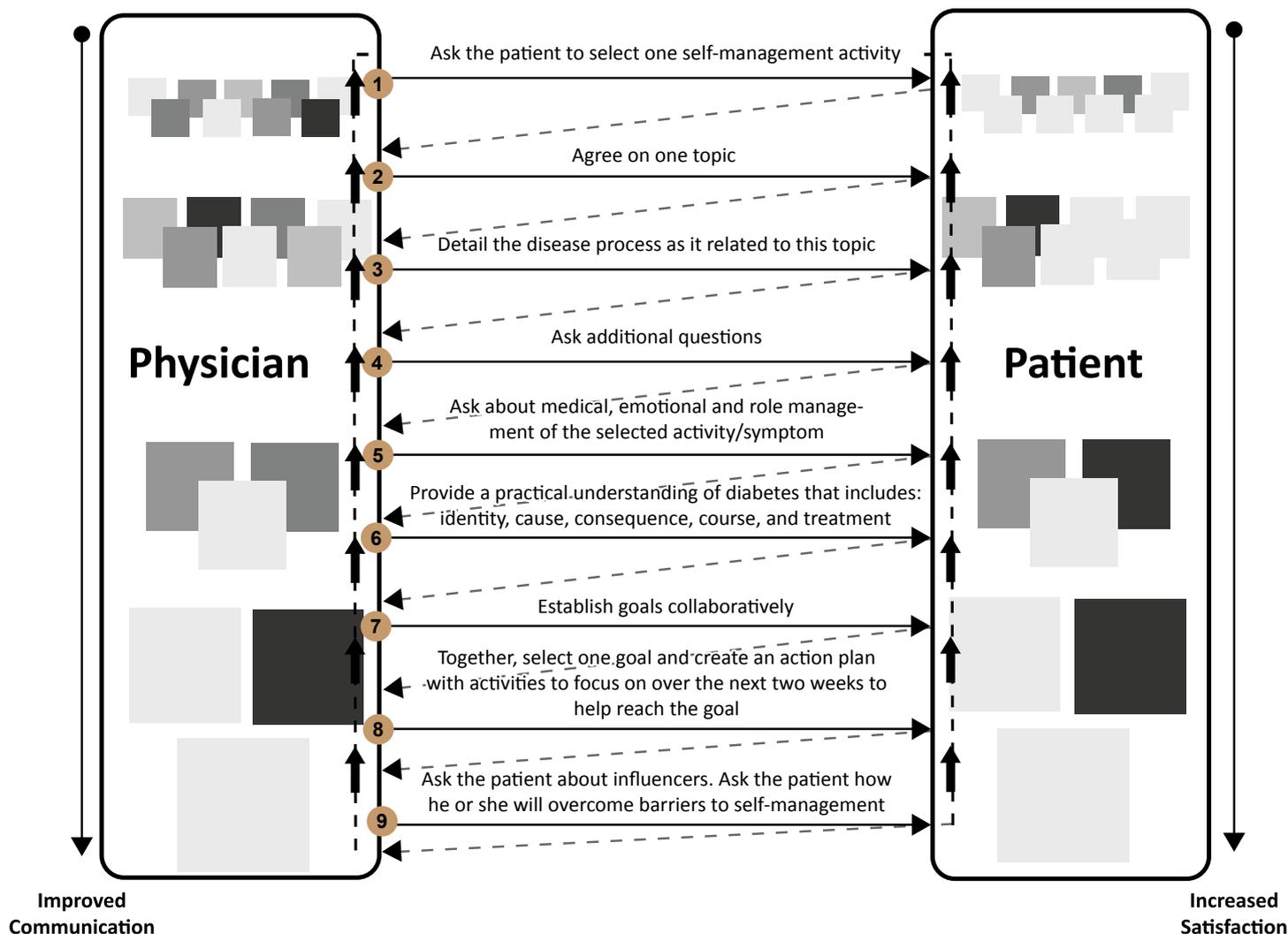


Figure 3. Summary of the patient and provider interaction to address self-management.

Successful self-management benefits patients and healthcare providers. For this, physicians should play a strong supporting role in helping the patients take center stage in controlling diabetes. ■

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## FEATURED ARTICLE

## Diabetes in India: The Current Scenario

### Introduction

The prevalence of diabetes in India is increasing.<sup>1,2</sup> Currently, India is the country with the second largest number of diabetic patients in the world, with China holding the first position.<sup>1,3</sup> Also, it should be noted that India is the second most populous country in the world, second only to China. By the year 2030, it has been predicted that India will have 79 million patients with diabetes. The increase in the prevalence of diabetes in the country, specifically type 2 diabetes, could be attributed to the increasing prevalence of central obesity, growing urbanization, declining physical activity and extensive use of calorie-rich foods.



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### Why is India an Obvious Target for the Diabetes Epidemic?

The economic growth of India is impressive with the GDP clocking a frenetic growth rate during the last five years. This contributes to further augmentation of purchasing power and consumer spending in the country. This economic growth has also seen the increasing westernization of the Indian population. Dietary patterns are changing. Spending on food items is increasing and lifestyles are increasingly becoming sedentary. Earlier, infectious and parasitic diseases were very common among Indians. However, significant medical advances have served to control these diseases, and this has ushered in an era of increasing appearance/prevalence of non-communicable diseases like diabetes, obesity, hypertension, cancer, and heart diseases. Increasing urbanization also plays a role.<sup>4</sup> It has been reported that by the year 2030, about 46% of Indian population will live in cities. Urbanization further leads to an increase in junk food intake, mental stress, and decrease in opportunities for physical activity. Together, this is a potent cocktail that threatens to implode into a diabetes epidemic for India.

The two hypotheses, the thrifty phenotype hypothesis and the thrifty genotype hypothesis proposed for addressing the etiology of type 2 diabetes, better explains the increase in disease prevalence seen among Indians.

- The phenotype hypothesis suggests that maternal malnutrition and low birth weight in Indian children make them susceptible to respond differently to a Western lifestyle. In the mother's womb, the nutritionally deprived baby tends to store whatever food it receives as fat. In adulthood too, man emulates this learned behavior. However, with increasing calorie consumption, given that the percent of fat intake remains the same, the absolute amount of calorie that is converted into fat has now increased. This fat gets deposited in the abdominal region, and is termed abdominal, visceral, or central fat. Central fat is highly toxic, and produces a set of chemicals called 'adipokines', which oppose the action of insulin, contributing to the development of diabetes. The mechanism responsible for diabetes also sets in an epidemic of hypertension, high cholesterol, and heart disease, together referred to as the 'metabolic syndrome' or the 'insulin resistance syndrome'.
- The thrifty genotype theory is somewhat similar, except that it suggests that Indian genes seem to produce a tendency to store fat, a response that is learnt from repeated periods of starvation and famines that have occurred

in India over the last several centuries. This ‘thrifty’ fat storing gene, which is an advantage during the famines, actually turns dangerous in times of plenty, and a lot of food gets stored as fat, with the same disastrous complications of the metabolic syndrome.

### Prevalence of Diabetes in India

The prevalence of diabetes in India varies between regions. The National Urban Diabetes Survey data published in 2001 showed that the age-standardized prevalence of diabetes in the Indian population is 12% (Figure 1).<sup>4, 6</sup> The prevalence of diabetes in the metropolitan cities in India is very high, with the highest prevalence of 18.6% reported from Chennai.<sup>2, 6, 7</sup>

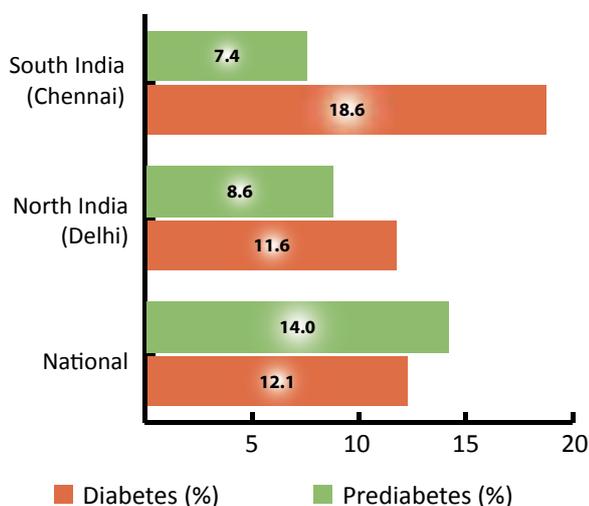


Figure 1. Prevalence of type 2 diabetes in India

In rural India, which is fast getting urbanized, the prevalence of diabetes is increasing.<sup>7</sup> A study conducted in western India has reported a prevalence rate of 9.3% for diabetes in rural areas. Rural-to-urban migration also has increased the overall prevalence of obesity and diabetes in the country.<sup>8</sup>

### Key Predisposing Factors

It is well known that type 2 diabetes is associated with cardiometabolic risk. The term ‘cardiometabolic risk’ is used to describe the components of the metabolic syndrome, which tend to cluster with type 2 diabetes (Figure 2). The genesis of the metabolic syndrome is not well understood; although many hypotheses have been proposed.<sup>9</sup> Emerging evidence consider non-alcoholic fatty liver disease (NAFLD) and polycystic ovarian disease (PCOD) as part of this syndrome. The prevalence of cardiometabolic risk factors including higher cholesterol/lipid levels, hypertension, abdominal obesity, cardiovascular risk, and risk of coronary artery disease is increasing exponentially in Indians, particularly among children and adolescents.

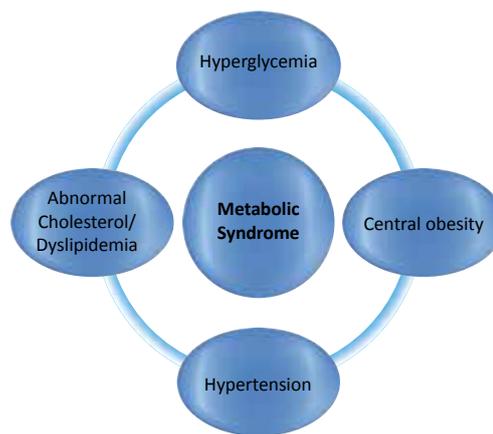


Figure 2. The Metabolic syndrome is linked to type 2 diabetes and coronary artery disease.

Central adiposity/central obesity is considered as a key risk factor predisposing individuals to type 2 diabetes. Indians are susceptible to diabetes risk at lower levels of central obesity when compared to Westerners. The waist circumference (WC) is a good measure of central obesity. Cutoff values for a normal WC in male and female Asian Indians are 85 and 80 cm, respectively. Higher values indicate a higher risk of the metabolic syndrome. Notably, these values are higher than cutoff values recommended for Western population.

Diabetes occurs 10-15 years earlier in Indians as opposed to individuals of non-Indian origin.<sup>10</sup> It has also been reported that Indian patients with diabetes are leaner than their western counterparts.<sup>11</sup> Also, increased prevalence of diabetic complications, like nerve disease, blindness, kidney disease, heart disease, and foot amputations, are all reported by Indian diabetic patients.

### How Well are Indian Diabetics Controlled?

The blood sugar control in India is generally suboptimal. Even with treatment, the glucose levels are not regulated effectively. Modifications in treatment to optimize the blood sugar level are often delayed, thereby increasing the risk of patients to develop diabetes-related complications. There are several challenges to diabetes management in India.<sup>12</sup> Generally, by the time the insulin is started, nearly 40% of these patients would have developed a diabetic complication.<sup>13</sup> Recently, there has been an increasing focus on HbA1c as the best test for assessing diabetes. The HbA1c test, which gives an assessment of glucose control over the last 3 months, is currently being recommended for the diagnosis of diabetes. The cut-off HbA1c level for the diagnosis of diabetes is >6.5%. In subjects, who are already known to have diabetes, the HbA1c should be kept below 7%. In Indian patients, by the time insulin therapy is started, the HbA1c level would have reached

9.3%.<sup>13</sup> This indicates the sub-optimal nature of glycemic control in India.

### What is the Cost of Treating Diabetes in India?

The financial burden attributed to diabetes is huge and it includes direct and indirect costs. The term direct costs denote the expenses borne by the patient, family members, and the health authorities. Indirect costs are larger and they include declining ability to work, sickness absenteeism, premature retirement, associated diseases, and even premature death. It has been estimated that the average Indian would have to spend ₹6,260 in rural areas and ₹10,000 in urban areas, annually. In general, people with diabetes would incur a 2- to 5-fold increase in medical expenditure. According to a 2008 review, the total annual cost of diabetes care in India is attributed to be around ₹180,000 million.<sup>2</sup>

### What are the Treatments Available in India?

Almost all the medications indicated worldwide currently for diabetes management is available in India. Oral drugs called sulfonylureas improve insulin production, while drugs, like metformin and pioglitazone, act by increasing insulin action. The discovery of 'incretins' have opened up a new avenue for diabetes therapy. Incretins, belonging to the group of gastrointestinal hormones, play a key role in stimulating pancreas to produce more insulin. The two major clinical candidates belonging to this group are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP). With the discovery of incretins, a new group of diabetic drugs namely incretin mimetics have emerged; one among these is exenatide (needs twice daily injections). The efficacy of the drug in lowering blood glucose as well as in achieving weight reduction has been proven through several studies. The other incretin mimetic that is available in India is liraglutide. The effect of liraglutide is touted to prolong up to 24 hours after a single injection. Although transient, the major side effects of this group of medicines are nausea and vomiting. In addition to incretin mimetics, newer drugs that can increase the body stores of incretins are also available. Some of the examples of these orally administered medications are sitagliptin and saxagliptin.

### Role of Artificial Pancreas in Achieving Glycemic Control

The crudest form of an artificial pancreas is an insulin pump. The pump is a pager-sized device that delivers insulin 24 hours a day by tubing into a port under the skin. These pumps deliver insulin in a pattern that

closely simulates pancreatic insulin production. Glucose control, in the author's experience, is very superior with pump therapy. However, not all patients are suitable for pump therapy. A qualified specialist is required to choose the right patient for insulin pump treatment. The next generation pumps are wirelessly hooked to a glucose-sensing device, which predicts hypoglycemia trends of the diabetics. This aids the patient to program the dosage of insulin based on his/her lifestyle. The future is likely to see the use of completely autonomous pumps, which can detect glucose levels and adjust insulin release proportionately to the blood glucose levels. Some of the pumps may even be implanted into the abdomen.

### Strategies to Contain Diabetes Prevalence

The diabetes epidemic in India is a complex problem, and seeks solutions that are equally complex.<sup>14</sup> Diabetes can be prevented by diet control, exercise, and medications. Among medications, metformin, a drug that improves insulin action, has been shown to prevent diabetes in a landmark study called the Indian Diabetes Prevention Program.<sup>15</sup> However, lifestyle changes are more important than prescribing/administering drugs.

It is important to target obesity in children and adolescents, as this is often a forerunner to diabetes as well as hypertension.<sup>16,17</sup> It has been shown that obese children have higher levels of cardiac- and diabetes-related risk markers. Increasing the physical activity in schools as well as the promotion of healthy eating patterns will all go a long way in diabetes prevention in children.

School health initiatives/activities are a priority. The prevention of childhood obesity is an urgent need. Conducting educational programs and interactive classes on physical education, as well as improving sport-related infrastructure in schools, is a pressing need of the hour. For obese youngsters and adults, avenues for physical exercise must be available in urban India. This includes playgrounds, pavements, and special consideration given to cyclists and joggers in the urban traffic planning. For those diagnosed with diabetes, a national program for uniform diabetes care is important, with free basic diabetes care made available to the needy in the country. Increasing public awareness and conducting continuing medical education programs on diabetes management for healthcare professionals are also necessary.<sup>18</sup> These programs should be aimed at increasing awareness about the diagnosis and comprehensive management of diabetes and its complications. ■

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## Type 2 Diabetes in India: An Epidemiological Overview



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### Introduction

The rapid rise of noncommunicable diseases (NCDs) represents one of the key challenges to global development in the new century. Indeed, they have emerged as major concerns in South Asia.<sup>1</sup> The rising prevalence of diabetes is becoming a global concern. The disease burden, attributed to morbidity, mortality, and reduced quality of life, is reported to be substantial, particularly among the earning age group.<sup>3</sup> Compared to type 2 diabetes, which accounts for over 90% of cases globally, frequency of type 1 diabetes is relatively low (~10%). Type 2 diabetes currently affects 6.6% of the world's adult population, with almost 80% of the total being in developing countries.<sup>4</sup> The disease, which affects the poor and young in developing countries disproportionately, is reported to have a significant negative impact on the productivity and economy of these countries.<sup>5</sup>

According to a previous estimate, the increased prevalence of chronic diseases contributes to 44% loss of disability-adjusted life years and 53% of deaths in India.<sup>1</sup> Diabetes has been known for many centuries, but diabetes epidemiology is relatively young in India.<sup>2</sup> As per the International Diabetes Federation (IDF) estimates, the total number of diabetic patients in India is around 50.8 million and these numbers are expected to increase to a staggering 87.0 million by 2030.<sup>4</sup> Studies have shown that prevalence rate of diabetes is soaring in urban areas, and in the peri-urban population the prevalence rate is found to be intermediate between the rural and urban populations.<sup>6</sup> The increase in prevalence is mainly attributed to urbanization, industrialization, and globalization.

### National Studies on Prevalence of Diabetes

Epidemiology of diabetes in India has a long history. A few attempts were made in the first quarter of 20<sup>th</sup> century to study the prevalence of diabetes in India. However, due to variability in sample selection, methods of screening, and diagnostic criteria used; the data available was not uniform. Some of the epidemiological studies and population-based surveys conducted in late 90s and the present century provided ample data to clearly analyze the diabetes prevalence in the country.<sup>7</sup>

A multicentric collaborative study undertaken by the Indian Council of Medical Research (ICMR) in 1970s to obtain diabetes prevalence rates in 6 different parts of the country (Ahmedabad, Kolkata, Cuttack, Delhi, Pune, and Trivandrum) reported the prevalence of diabetes to be 2.1% in urban and 1.5% in rural areas.<sup>8</sup> In the same study, the prevalence reported in individuals above 40 years of age was 5% in urban and 2.8% in rural areas.<sup>8</sup>

The second national level population based study, called the National Urban Diabetes Survey (NUDS), was conducted in the year 2001, in six large cities. The study performed on 11,216 subjects aged  $\geq 20$  years reported the age-standardized prevalence of type 2 diabetes as 12.1%, with no gender difference. The highest rate of prevalence was in Hyderabad (16.6%), followed by Chennai (13.5%), Bengaluru (12.4%), Kolkata (11.7%), New Delhi (11.6%), and Mumbai

(9.3%).<sup>9</sup> The data obtained from the national study demonstrated that the prevalence of diabetes is relatively high in the urban metros of India.

Later in 2004, the Prevalence of Diabetes in India Study (PODIS), a random multistage cross-sectional population survey, was carried out in subjects aged  $\geq 25$  years in urban and rural India. The diabetes mellitus prevalence was defined using the WHO and ADA criteria.<sup>10, 11</sup> To assess the prevalence using ADA criteria, 41,270 subjects were recruited from 108 centers (49 urban and 59 rural); and for evaluation using WHO criteria, 77 centers (40 urban and 37 rural) were included and 18,363 subjects were studied. Based on ADA criteria, the prevalence of diabetes was 4.7% in the urban and 1.9% in the rural areas.<sup>10</sup> Whereas, the prevalence reported using WHO criteria was 2.7% and 5.6% among rural and urban areas, respectively.<sup>11</sup>

Reliable surveillance data are crucial for determining public health priorities as well as monitoring the progression of preventive efforts. With this in view, a Sentinel Surveillance System for cardiovascular disease (CVD) was carried out in Indian industrial populations.<sup>12</sup> This study, which was done in 10 centers from different parts of the country, reported prevalence of diabetes to be 10.1% and that of self-reported diabetes to be 5.6%. Another NCD Risk Factor Surveillance study conducted in different regions (east, south, north, west/central) of India demonstrated that the overall prevalence of self-reported diabetes was higher in southern states (Trivandrum=9.2%, Chennai=6.4%) compared to the north (Delhi=6.0%, Ballabgarh=2.7%), east (Dibrugarh =2.4%) and west/central India (Nagpur=1.5%).<sup>13</sup> Based on the residential areas, this study showed that the lowest prevalence of self-reported diabetes was observed in rural (3.1%) followed by peri-urban/slum (3.2%), while the highest prevalence was seen in urban areas (7.3%).

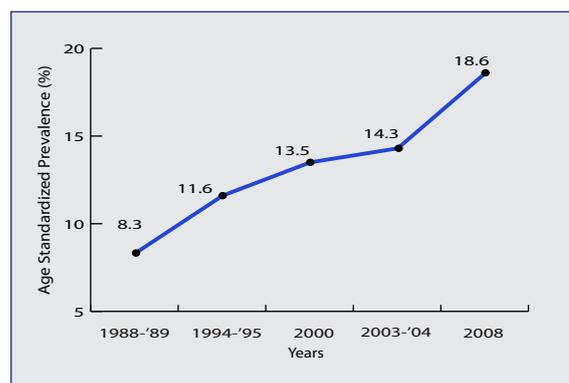
From the above studies, which provide clear evidence on the secular trends across different parts of the subcontinent, it can be concluded that the prevalence of diabetes in India is escalating rapidly both in the urban and rural areas. Thus, these data provide an updated quantification of the growing burden of diabetes in the subcontinent during the past three decades.

**Regional Studies on Prevalence of Diabetes**

In South India, many population-based studies have been done during the past 3 decades to obtain the prevalence of diabetes.<sup>14-21</sup> The Chennai Urban Population Study (CUPS), involving two residential areas denoting the

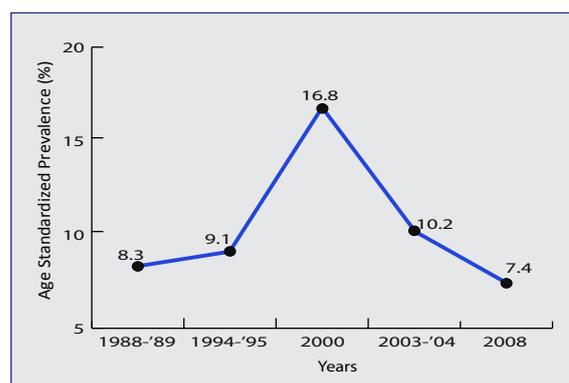
low- and middle-income groups, was taken up in urban Chennai (formerly Madras) in 1996.<sup>18, 22</sup> Among the 1,262 subjects studied, 12% of the total population had diabetes. The study results showed a substantially increased age-standardized prevalence rate of diabetes in the middle-income group as opposed to the low-income group (12.4% vs. 6.5%, respectively). CUPS showed that there are intra-urban differences in the prevalence of diabetes even within a city.<sup>18</sup>

The Chennai Urban Rural Epidemiology Study (CURES) was carried out in 2001 and involved a representative sample of 26,001 subjects from Chennai. This facilitated comparisons with previous estimated rates of diabetes in Chennai city with three earlier population-based studies carried out in Chennai using similar methods.<sup>9, 15, 16</sup> The age-standardized diabetes prevalence, reported in CURES, based on WHO criteria, was 14.3%.<sup>19</sup> The following graph shows the diabetes prevalence noted in different periods in Chennai (Figure 1A).



**Figure 1A:** Trends in the prevalence of diabetes at Chennai (1988-2008)<sup>19, 21</sup>

From the above figure, it is evident that within a span of 14 years, the prevalence of diabetes increased significantly by 72.3 %.<sup>21</sup> However, a decrease in prevalence rate of impaired glucose tolerance (IGT) was reported during the CURES when compared to previous studies (16.8% in 2000 to 7.4% in 2008) done in Chennai (Figure 1B).<sup>9, 19, 21</sup>



**Figure 1B:** Trends in the prevalence of IGT at Chennai (1988-2008)<sup>19, 21</sup>

This suggests that the diabetes epidemic in urban India may be slowing down or it could also suggest that there could be a rapid progression from the normal state through IGT to diabetes.

Another community-based cross-sectional survey, the Amrita Diabetes and Endocrine Population Survey (ADEPS), done in urban areas of Ernakulam district in Kerala, also revealed a very high prevalence of newly detected diabetes (10.5%), and lower prevalence of impaired fasting glucose (7.1%) and IGT (4.2%).<sup>20</sup> A very recent community-based survey conducted in Manipal, Karnataka, among adults aged  $\geq 30$  years, reported high prevalence of diabetes among coastal population of Karnataka (16%).<sup>23</sup>

In the eastern region of the subcontinent, the prevalence in urban areas showed a rise from 2.3% in 1975 to 11.7% in the year 2001.<sup>9,24</sup> A study by Shah et al done in urban areas of Guwahati (1998) reported the prevalence of diabetes to be 8.2%, while another study conducted in peri-urban population of Manipur by Singh et al (2001), reported the prevalence to be 4.0%.<sup>25,26</sup> However, there are very few studies evaluating the disease prevalence in the eastern part of the country. Also, most of these studies have been carried out in metros alone, or only in small villages or towns.<sup>9-11.</sup>

Studies in the western part of India have been conducted in Mumbai, Thane, and Ahmedabad. The prevalence of diabetes in Mumbai in the year 1963 was reported to be 1.5%.<sup>27</sup> In 2001, the prevalence in the urban Dombivli population, was 6.15%, and 9.3% among Mumbai population.<sup>9,28</sup> Studies in the rural areas of Western India reported an escalation of diabetes prevalence from 3.9% in 1991 to 9.3% in 2006.<sup>29,30</sup>

Also, in northern parts of India, an increasing trend in the prevalence rates of diabetes is noted since mid 1960s. In mid 60s, the prevalence rate in Chandigarh was 2.9%. Misra et al reported a prevalence of 10.3% in an urban slum area in Delhi.<sup>31,32</sup> In two studies (2000 and 2001) conducted in the Kashmir valley, the prevalence of the disease in adults aged  $\geq 40$  years was found to be around 8%; among whom, three-fourth of the cases were undiagnosed.<sup>33,34</sup> In a recent study conducted to determine the prevalence of type 2 diabetes in 3,024 subjects of the younger age group (20–40 years) in the same area, the age-adjusted prevalence of diabetes was reported to be 2.4%.<sup>35</sup> In the Jaipur Heart Watch studies 2 and 4 conducted in 2002 and 2007, respectively, the corresponding prevalences of diabetes was reported

to be 12.2% and 20.1%.<sup>36,37</sup> In rural areas of Delhi and Nagpur, the corresponding prevalence rate was 1.5 % (1991) and 3.7% (2007).<sup>38,39</sup>

### Reasons for Increasing Diabetes Prevalence in the Subcontinent

The factors implicated for the causation of diabetes in Asian Indians are age, gender, lower birth weight, migration diet, physical inactivity, ethnic susceptibility and genetic factors, increased stress, and insulin resistance. It has been observed that diabetes in India occurs a decade earlier than in the developed world, as shown by the Daryaganj survey, NUDS and CURES, although the prevalence peaks at an older age.<sup>9,19,40</sup> The peak age prevalence was found to be in the age group of 60-64 years in the Daryaganj survey, and 60-69 years in NUDS and CURES.

Diabetes is increasing in developing countries like India and the main contributing factors are change in diet and decreased physical activity. In South Asian countries, the diet pattern is shifting from traditional diets towards diets with excess calories and/or sugar and fat intake. Recently, we showed that refined cereal, particularly white rice, adds to the glycemic load and thus contributes to diabetes and metabolic syndrome in Chennai.<sup>41,42</sup>

The NUDS and the CUPS revealed a rising prevalence of diabetes with increasing family income, which may be related to the richer diets associated with higher incomes.<sup>9,18</sup> When the study participants were randomized, based on the occupation during NUDS, the maximum prevalence of diabetes was reported among the unemployed and retired subjects. Prevalence of diabetes was significantly lower in those in the highest quartiles of physical activity (11.0%) compared to those in the lowest quartile (16.8%). Similar study results were obtained during CUPS, which documented that the prevalence of diabetes was higher among subjects undergoing light-grade activity (17.0%) in contrast to those performing moderate-grade (9.7%), and heavy-grade physical activities (5.6%).<sup>43,44</sup>

From the above data, it can be attributed that exercise plays a crucial role in preventing the development of diabetes. Changes in diet and physical activities are thus some of the key factors contributing to increasing obesity and type 2 diabetes rates in India.

### Conclusion

Convincing evidence has emerged over the past two decades that there are regional differences in the prevalence of diabetes. These estimates vary by area:

urban, rural, or peri-urban, but generally a higher prevalence of diabetes is observed in urban areas and a lower prevalence in rural areas with intermediate rates in peri-urban areas. This appears largely due to variation in socioeconomic factors. Moreover, the estimates of diabetes vary substantially across populations due to variability in sample selection, methods of screening, and diagnostic criteria used. The rising trend of higher prevalence of diabetes observed even among younger age groups in Indians is of particular concern, as it means that they will have more prolonged exposure to cardiovascular risk factors and complications associated with diabetes.

As diabetes is an asymptomatic disorder, early identification of individuals at risk and appropriate lifestyle interventions will greatly help to prevent or delay the onset of diabetes and thereby reduce the burden of complications due to diabetes in India. ■

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## High Glycemic Index Foods Increase Heart Disease Risk in Women

It is well known that a diet rich in cholesterol and saturated fats increases the risk of coronary heart disease (CHD) by inducing atherosclerosis. Recent research has focused on the other constituents of the diet, such as carbohydrates, and their role in CHD. One such study published in the latest issue of *Archives of Internal Medicine* reports that foods containing carbohydrates with a high glycemic index (GI) increase the risk of CHD in women, but not in men.

The study conducted by Sabina Sieri from the Nutritional Epidemiology Unit, Fondazione IRCCS, Milan, Italy, and co-researchers, provided a dietary questionnaire to 47,749 volunteers comprising of 32,578 women and remaining men, originally enrolled into the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The adjusted relative risks (RRs) and 95% confidence intervals (CI) were estimated using the Multivariate Cox proportional hazards model.

A total of 463 CHD cases were diagnosed during the median follow-up period of 7.9 years, of which 158 were women. Findings of the study include:

- A significantly increased risk of CHD was observed in women who consumed the highest amount of carbohydrate compared to women who consumed the lowest amount of carbohydrate (RR=2.00; 95% CI=1.16-3.43).
- Increasing the consumption of foods rich in carbohydrates with a high GI, and not carbohydrates with low GI, increased the risk of CHD (RR=1.68; 95% CI=1.02-2.75).
- Women with a high glycemic load (GL) were associated with a significantly higher risk of CHD, compared to those with a low GL (RR=2.24; 95% CI=1.26-3.98).

None of the above associations were found in men.

GI is a rating system for foods, based on the extent to which they raise blood sugar levels in the two hours following consumption. Foods are scored on GI by comparing them against a standard, which is usually pure glucose or white bread, having an arbitrary score of 100. A food item with a high GI releases carbohydrates (in the form of glucose) into the bloodstream more rapidly than a food item with low GI. A GI score of 70 and above (e.g. corn flakes, instant white rice, baked potato) is considered high, 56 to 69 (rye bread, macaroni and cheese, ice cream) medium, and 55 (ripe banana, steamed brown rice, apple, yogurt, milk, peanuts) as low.

Foods with high GI produce rapid insulin response, which in turn causes a reactive relative hypoglycemia during the postprandial period. The hypoglycemia induces an increase in appetite and higher food consumption, which may cause weight gain and obesity. Hyperinsulinemia, induced by a diet rich in high GI foods, has been associated with a higher risk of ischemic heart disease. In men aged 45 to 76 years, when the fasting glucose level increases by one standard deviation, the odds ratio of developing ischemic heart disease increases by 60%.

Glycemic load is calculated by multiplying glycemic index by the grams of carbohydrate per serving, and dividing this by 100. A glycemic load of >10 is considered high. GI is a measure of carbohydrate quality (source or nature), whereas GL is a measure of carbohydrate quantity, i.e., the net glycemic effect of a portion of food.

The GI and GL of some common foods are given below.

Food Item	Glycemic Index	Serving Size (in gram)	Glycemic Load
Cornflakes	92	30	23.9
Baked potato	85	110	20.3
Carrot	71	55	3.8
Ice cream	61	50	7.9
Peanut butter sandwich	59	100	26
Macaroni and cheese	54	180	32.6
Ripe banana	51	120	12.9
Grapes	46	120	8.3
Spaghetti	41	55	16.4
Apple	36	200	3.2

Table adapted from Last AR, Wilson SA. Low-carbohydrate diets. *Am Fam Physician*. 2006 Jun 1;73(11):1942-8.

According to the Centers for Disease Control and Prevention (CDC), CHD, generally believed to be a 'man's disease', causes nearly equal number of deaths in men and women. In American women, it is the leading cause of death, with a mortality rate of 26%. Physical inactivity, unhealthy diet, smoking and obesity are some of the major risk factors for heart disease in women. The results of the current study further emphasize the need for enlightening the general population on the role of a healthy diet in preventing CHD, and choosing the right type of carbohydrate (with low GI and GL), especially in women. ■

References available online at [www.medinewsdirect.com](http://www.medinewsdirect.com)

## Inhibition of LDL Recognition by T cells Suggested as a Strategy for Atherosclerosis Vaccine

Numerous studies have proposed that the immune reaction to oxidized low-density lipoprotein (oxLDL) plays a crucial role in the different phases of atherosclerosis. Reporting that T cells attack normal LDL rather than the oxLDL molecules, a recent breakthrough study suggests that blocking the LDL-recognizing T cell receptors could seize the T cell's response to LDL, thereby conferring protection against atherosclerosis. The findings of the study are published in the recent issue of *The Journal of Experimental Medicine*.

In order to investigate the mechanism of recognition that directs T cell's response to LDL, Göran K Hansson, professor of experimental cardiovascular science at the Karolinska Institutet, Sweden, and co-workers, created T cell hybridomas with human apolipoproteinB100 (ApoB100) transgenic (huB100tg) mice, which were immunized with oxLDL of humans. The following findings were noted during the study:

- CD4+ T hybridoma cells responded to native LDL and purified apolipoprotein ApoB100, but not to oxLDL
- Sera of the immunized mice showed the presence of oxLDL-specific IgG antibodies, suggesting that the response of T cells to native ApoB100 could probably aid B cells in developing these antibodies against oxLDL
- Hybridoma cells responding to ApoB100 were restricted to MHC class II, and expressed a single T cell receptor variable (V)  $\beta$  chain (TRBV31), along with diverse V $\alpha$  chains
- Immunizing huB100tgxLdlr<sup>-/-</sup> mice with TRBV31-derived peptide resulted in the induction of anti-TRBV31 antibodies, which blocked the recognition of ApoB100 by T cells. This helped reduce atherosclerosis by 65%, while simultaneously decreasing MHC class II expression and macrophage infiltration in the lesions.

Based on these results, the researchers concluded that the obstruction of T cell receptor-dependent recognition of epitopes on the native ApoB100 protein could be an effective vaccination strategy against the chronic inflammatory disease. The results are anticipated to explain the ineffectiveness of antioxidants against atherosclerosis, since it is presumed that antioxidant intake reduces the risk of this cardiovascular disease by preventing LDL oxidation.

Several other strategies had been proposed earlier for developing vaccines for atherosclerosis. In one such study, Shah et al (*Nature Reviews Cardiology*, 2005), identified numerous antigenic epitopes in the human apoB100 constituent of LDL cholesterol. Active immunization with a few of these epitopes lowered atherosclerosis in hyperlipidemic mice models. Based on the results, the researchers hypothesized that the designing of a vaccine based on apoB100-associated peptide could aid in atherosclerosis reduction.

Immunization against tyrosine kinase with Ig and epidermal growth factor (EGF) homology domains 2 (TIE2[+]) cells, which play a significant role in processes involved in atherosclerosis, has been suggested as another potential strategy for vaccine development by Hauer et al (*Atherosclerosis*, 2009).

Atherosclerosis of coronary arteries, which leads to coronary heart disease (CHD), is the leading cause of death in the United States. According to the 2009 update provided by the American Heart Association, approximately 795,000 people would experience a new or recurrent stroke annually. Of these cases, around 610,000 are first attacks and 185,000 are recurrent attacks.

With the current findings being successful in animal models, further exploration and validation on the vaccine's safety, durability, and optimal route of administration in humans, could make immune modulation a potential treatment strategy for preventing atherosclerosis, and reducing the risk of CHD and associated cardiovascular diseases. ■

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## Diabetes Linked to Enhanced Risk for Second Primary Contralateral Breast Cancer

Previous studies have suggested a direct association between hyperinsulinemia and mammalian carcinogenesis. Now, a recent population-based nested case-controlled study, published in the journal *Breast Cancer Research and Treatment*, is touted as the first research suggesting an elevated risk for contralateral breast cancer (CBC) in diabetics diagnosed with primary breast cancer.

Christopher I Li and colleagues from the Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, Washington, evaluated the association between diabetes and CBC in 40 to 79-year-old patients diagnosed with estrogen-receptor positive invasive breast cancer. The study group comprised of 322 women diagnosed with second primary CBC, while 616-matched patients diagnosed with the first incidence of breast cancer served as controls.

Conditional logistic regression analysis showed that the risk for developing CBC was 2.2 times higher (95% CI=1.3-3.6) in diabetics as opposed to subjects without a previous history of diabetes. Additionally, the risk was found to be more prominent among patients detected with their first incidence of breast cancer before 60 years of age (OR=11.5; 95% CI=2.4-54.5), in contrast to those diagnosed with the malignancy at  $\geq 60$  years of age (OR=1.5; 95% CI=0.8-2.7).

An earlier review by Michels et al (*Diabetes Care*, 2003) reported a slightly elevated risk for developing breast cancer in type 2 diabetics, based on the prospective evaluation conducted among 116,488 female nurses aged between 30 to 55 years. The risk was found to be pronounced in postmenopausal women, but not in premenopausal subjects.

The major mechanisms contributing to the diabetes and breast cancer association are as follows:

- Activation of the insulin-IGF-1 pathways
- Altered regulation of endogenous sex hormones
- Altered regulation of adipocytokine levels

Analysis of various comparative cohort studies and case-control studies concluded on the following, in relation to the association:

- Type 2 diabetes is linked to 10-20% elevated risk for breast cancer
- Breast cancer is associated with gestational diabetes, but not with type 1 diabetes
- Diabetes and the associated co-morbidities could have an adverse impact on screening utilization and oncology therapies
- Some of the potent antidiabetic drug classes, including peroxisome proliferator-activated receptor  $\gamma$  ligands and biguanides, are reported to confer protection against breast cancer. Such therapeutic effects are being investigated in clinical trials

Further substantiation of the association could be crucial in recommending screening in diabetic breast cancer survivors. Another recent study by Schott et al (*Experimental and Clinical Endocrinology & Diabetes*, 2010) reported that such studies should be directed towards investigating ways of ruling out possible overlapping of pathomechanisms, therapeutic interactions, prognostic factors as well as interactions (synergistic, additive or controversial) in chemotherapy and diabetes drugs. ■

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## Studies Report Enhanced Adenoma Detection with Third Eye Retroscope

Colonoscopy has emerged as the preferred screening test for colorectal cancer. However, there is an increased chance for missing the lesions due to increased difficulty in detecting them if located in the proximal part of folds or flexures, using a forward-viewing colonoscope. Now, five studies presented at the recent Digestive Disease Week® 2010 conference (DDW) held at New Orleans, further substantiate the efficacy of Third Eye® Retroscope® (TER) developed by Avantis Medical Systems in detecting adenomas of varying sizes in both young and adult population.

One of the studies presented by Luis F Lara from the Baylor University Medical Center, Dallas, Texas, investigated the rates of detecting adenoma and all polyps using TER in contrast to the forward-viewing colonoscope, along with the evaluation of learning curve for the use of TER. During the study, patients who had previously undergone colonoscopy were categorized into three groups based on the time interval between earlier and current colonoscopy: <2 years (Group 1), between 2 to 6 years (Group 2), and >6 years (Group 3).

For each group, the researchers analyzed the polyp and adenoma detection rates using colonoscopy alone, and in conjunction with TER. In 298 study participants, 164 screening, 72 diagnostic, and 62 surveillance colonoscopies were performed. The key findings were as follows:

- TER contributed to a substantial increase in the overall polyp detection rates by 12 to 18%, and the adenoma rates by 13 to 19%
- The number of polyps removed from the surveillance group was 58; among these 37 (64%) were identified as adenomas
- TER, in contrast to colonoscopy alone, contributed to improved detection of 11% and 30% more polyps in Group 1 (no adenomas), and Group 2 (33% more adenoma), respectively
- In Group 3, no additional polyps were identified using TER

Based on the study findings, the researchers concluded that the use of TER in patients undergoing screening, diagnostic, and surveillance colonoscopy augmented the detection rates for both adenomas and all polyps. The most significant benefits were reported in Group 2 patients.

Another study presented at the same conference by Manoj K Mehta, from the NorthShore University HealthSystem, Illinois, analyzed the influence of the investigators' cumulative years of experience in detecting baseline adenomas through the same two techniques. Around 15 physicians from nine centers took part in the study, and were categorized into groups of 1-10, 11-20, 21-30, and 31+ years, based on their cumulative years of experience. The researchers noted that the highest clinical accuracy for detecting baseline adenomas using standard colonoscopy, and the increased detection rates using TER were shown in the 11-20 year group.

The new device helps in providing improved colonoscopic visualization through the retrograde view and the illumination of blind spots in the colon. Other key features of the FDA 510(k) cleared TER are as follows:

- Disposable
- Equipped with a miniature camera and light source, which functions along with the standard colonoscope
- Aids in getting a retrograde view, which would complement the normal forward view obtained via a standard colonoscope
- Use of state-of-the-art technology, along with gold standard colonoscopy enables the introduction of TER through instrument channels of even the smallest colonoscopes
- Only system capable of delivering continuous retrograde view of the colon due to its potential to automatically turn 180 degrees and assume a 'J' position

**About Avantis Medical Systems, Inc:** Based in Sunnyvale, California, the company focuses mainly on the development of cost-effective devices that augment the detection and prevention of neoplasms affecting the gastrointestinal tract. ■

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## Study Reiterates Importance of Preimplantation Factor for Successful Pregnancy

Preimplantation factor (PIF), a 15 amino acid peptide secreted by viable embryos, is reported to play a crucial role in embryo implantation as well as achievement of maternal tolerance via local and systemic immunomodulation. Now, a recent genomic and proteomic study has provided further credence to the positive influence of PIF in embryo attachment and successful pregnancy. The findings have been published in the current edition of the *American Journal of Obstetrics & Gynecology*.

Michael J Paidas, from the Department of Obstetrics, Gynecology, and Reproductive Sciences, Yale University School of Medicine, Connecticut, and colleagues, investigated the impact of PIF on first-trimester decidua cultures (FTDC) and human endometrial stromal cells (HESC). HESC were decidualized with estrogen and progesterin, to imitate the preimplantation milieu. The trial involved the incubation of HESC or FTDC with 100 nmol/L synthetic PIF or vehicle control. Microarray and pathway analysis was used to determine global gene expression, quantitative mass spectrometry for proteins, and protein array for PIF binding.

The effects of PIF on diverse compounds/systems are depicted below.

- Impacts adhesion, immune system, and apoptotic pathways
- Substantial up-regulation of the following in HESC:
  - » Nuclear factor-k-beta activation via interleukin-1 receptor-associated kinase binding protein 1 (fold change=53)
  - » Down syndrome cell adhesion molecule like 1 (16)
  - » FK506 binding protein (15)
  - » 133kDa protein (2.3)
  - » Toll-like receptor 5 (9)
- Down-regulation of B-cell lymphoma protein 2 in FTCS (27.1) and HESC (21.1)
- Interaction of PIF with intracellular targets, insulin-degrading enzyme and beta-K<sup>+</sup> channels, as demonstrated by protein array

Based on the findings, the scientists concluded on the

multi-targeted effects of PIF in the regulation of adaptive apoptotic processes, promotion of embryo-decidual adhesion, and regulation of immunity.

The researchers reported similar findings with respect to the influence of PIF in enhancing immunomodulatory factors, particularly pro-inflammatory cytokines, chemokines and adhesion molecules, in an earlier study. PIF was also noted to increase protein expression like growth regulated oncogene-alpha, vascular endothelial growth factor, and monocyte chemotactic protein. These results support the role of PIF in maternal receptivity and implantation events.

Discovered by Eytan R Barnea, the founder of the Society for the Investigation of Early Pregnancy, New Jersey, PIF is present in the maternal serum and other body fluids following fertilization, before embryo implantation, and continues through the gestational period. The synthetic form of PIF was subsequently developed by Barnea, in replication of the native compound.

With research being conducted for decades to determine the essential factor needed for successful pregnancy, the researchers of the current study believe PIF to be the indispensable compound. More trials are currently in progress to ascertain the diagnostic potential of PIF for pregnancy viability in both humans and animals, owing to its presence in all mammals. PIF has also garnered further interest for its probable therapeutic uses in pregnancy, autoimmune diseases, and transplantation. ■

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## Influenza Vaccine Patch Containing Dissolvable Needles Developed

A team of researchers at the Emory University and Georgia Institute of Technology have designed a novel influenza-vaccine patch containing numerous vaccine-filled, dissolvable micron-scale needles, which facilitate painless intradermal administration. Enabling self-administration, the patch is reported to be easy-to-use, aiding in large-scale immunization programs, especially in developing countries. The promising findings of the study are published in the recent online publication of the journal, *Nature Medicine*.

Sean P Sullivan, at the Georgia Institute of Technology, Atlanta, and co-workers, conducted the study in three groups of mice: group I received the vaccine intramuscularly through conventional hypodermic needles; while group II and group III received the dissolving microneedle patches, with and without the vaccine (control), respectively, on their skin.

The three groups infected with influenza virus after 30 days of vaccination demonstrated the following findings:

- Group I and II, immunized with the vaccine, remained healthy. The vaccination was found to offer complete protection against the infection by stimulating both cellular and humoral immunity
- Group III suffered from influenza and experienced death

An additional group of mice was infected with flu virus three months after being immunized with dissolvable microneedle vaccination. With this, the group seemed to exhibit a better recall response to infection. It was also reported that microneedle vaccination, when compared to conventional intramuscular injection, eliminates the virus in lungs more effectively and offers improved cellular recall responses.

Based on these findings, the researchers suggested that the dissolving microneedle patches could make a safe and simpler vaccination strategy with enhanced immunogenicity, and eliminate the drawbacks associated with the use of hypodermic needles.

### Vaccine-patch design and its advantages

The vaccine patch consists of microneedles assembled into an array of 100, each 650 microns in length, and is made up of poly-vinyl pyrrolidone. The needle arrays were manufactured by mixing freeze-dried inactivated

influenza virus vaccine with vinyl-pyrrolidone monomer, followed by filling the mixture into the needle molds and polymerizing using UV light at room temperature. The dissolvable vaccine, when compared to the conventional ones, is found to have the following advantages:

- The vaccine being present in a dry formulation was stable during supply and storage.
- The pain associated with microneedle injection was non-existent to mild, and less than the conventional injection.
- On application, the microneedles got dissolved into the body fluids quickly, leaving behind only the water-soluble backing, which could help in easy disposal unlike the conventional injections, as it does not have any needle sharps.
- There are no needle sharps left over on the skin.
- The polymer material used in the needles is biocompatible.
- It enables self-administration, thereby eliminating the need for trained personnel for vaccination.
- It eliminates the risk of contracting dreadful infections such as HIV and hepatitis, associated with re-use of hypodermic needles.

Further to these advantages, numerous earlier studies have reported the safety and stimulation of long-term sustained immunogenicity with the use of microneedle patches. A review by Prausnitz et al (*Current Topics in Microbiology and Immunology*, 2009) reported that apart from the intradermal microneedle patch being safe and effective; it elicits the same immune response as intramuscular injection, at a lower dose. A recent study by Kim et al (*The Journal of Infectious Diseases*, 2010) showed that intradermal microneedle vaccination, when compared to the conventional intramuscular one, was superior in stimulating humoral as well as antibody-secreting cell immune responses following 100% survival from lethal challenges with the influenza virus.

With the current findings, it is indicative that the microneedle-vaccine patch technology could make a safe and effective alternative to the conventional injection procedures, and help reduce morbidity and mortality associated with vaccine-preventable influenza infections. ■

References available online at [www.medinewsdirect.com](http://www.medinewsdirect.com)

## Teriflunomide and Glatiramer Acetate Combination Safe and Effective Against Relapsing-remitting MS

The current long-term therapies used to treat multiple sclerosis (MS) are administered intramuscularly or subcutaneously, producing local adverse effects at the sites of injection. Hence, the development of an orally administered drug would offer greater convenience and be more acceptable to patients. Teriflunomide is one of five such orally administered disease-modifying agents (used against rheumatoid arthritis) currently under investigation. Now, a Phase II trial conducted by researchers at the Mount Sinai School of Medicine reports teriflunomide to be safe and effective when used in conjunction with glatiramer acetate for the treatment of relapsing-remitting multiple sclerosis (RRMS).

Aaron Miller, Professor of Neurology, Mount Sinai School of Medicine, New York, and colleagues, enrolled 123 patients with RRMS, already on glatiramer acetate into the study, and administered 7 mg/day or 14 mg/day teriflunomide for a period of 24 weeks, and placebo to a control group. All subjects were assessed through physical examination, laboratory reports and investigations including electrocardiogram, pancreatic ultrasound, and magnetic resonance imaging (MRI). The drug not only reduced the volume and size of the lesions in the brain, as detected by MRI, but also showed a high safety profile. Only seven treatment-related adverse effects necessitating treatment withdrawal were recorded.

Earlier studies have reported teriflunomide-related adverse events such as nasopharyngitis, nausea, alopecia, rise in alanine aminotransferase levels, diarrhea, arthralgia, paresthesias, and neutropenia. While discontinuation of treatment is not necessary, as these side effects may resolve on their own, the drug is associated with other rare but more serious adverse events including hepatotoxicity, trigeminal neuralgia, and rhabdomyolysis. Liver toxicity may be managed by regular monitoring of liver function, initially done monthly for the first 6 months, and once in 6-8 weeks thereafter.

Teriflunomide is an active metabolite of leflunomide, an

FDA-approved disease-modifying agent for the treatment of rheumatoid arthritis. The mechanism of action of teriflunomide is not yet clearly elucidated, but it is believed to have anti-inflammatory, immunomodulatory and anti-proliferative effects. It inhibits the enzyme dihydroorotate dehydrogenase, a crucial enzyme in pyrimidine synthesis, thus producing a cytostatic effect on B and T lymphocytes. The drug may also interfere with the interaction between antigen-presenting cells and T cells, which is vital for T cell immune response. In addition, teriflunomide is attributed to block tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )-induced nuclear factor kB activation, and inhibit matrix metalloproteinases and cell adhesion molecules.

According to the National Institute of Allergy and Infectious Diseases (NIAID), 250,000 to 350,000 individuals in the United States have MS as of 2009. MS is an inflammatory demyelinating disease affecting twice as many women as men. Some of the common symptoms include visual impairment, weakness, numbness, depression, dizziness and urinary incontinence. Magnetic resonance imaging with gadolinium contrast soon after the first attack provides clues to the diagnosis. It is important to rule out other diseases which may present with similar symptoms such as spinal cord compression, vascular disease, vitamin B12 deficiency, syphilis, systemic lupus erythematosus, and other inflammatory conditions. ■

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## Intensive Therapies for Hyperglycemia and Dyslipidemia may Reduce Diabetic Retinopathy Progression Rate

Earlier studies have substantiated the role of diverse systemic factors, including hyperglycemia, dyslipidemia, and hypertension, in the development and progression of diabetic retinopathy. Now, the results of a randomized trial, conducted by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group and ACCORD Eye Study Group reports that intensive glycemic control and a combination lipid therapy, using fenofibrate plus simvastatin, could be effective in reducing the rate of the progression of diabetic retinopathy. The study findings, published online in the *New England Journal of Medicine*, rules out the effect of intensive blood pressure regulation in attenuating the disease progression.

Emily Chew, chief of the Clinical Trials Branch of the Division of Epidemiology and Clinical Applications, National Eye Institute (NEI), and coworkers, conducted the study on 10,251 type 2 diabetes patients at an increased risk for cardiovascular disease. The subjects were randomized to receive intensive or standard treatment for hyperglycemia, dyslipidemia, and systolic blood pressure regulation. The target levels for the various systemic factors were as follows:

- Glycemic control: glycosylated Hb level= $\leq$ 6.0% for intensive treatment or 7.0 to 7.9% for standard treatment
- Blood pressure control:  $<$ 120 for intensive treatment or  $<$ 140 mm Hg for standard control

The intensive and standard treatment followed for dyslipidemia involved the administration of 160 mg daily of fenofibrate and simvastatin, or placebo in conjunction with simvastatin, respectively.

Using Early Treatment Diabetic Retinopathy Study Severity Scale, another small subset of 2,856 participants was investigated for the effect of these treatments on the progression of diabetic retinopathy after four years. The researchers also evaluated the development of the disease in these subjects by assessing the need for laser photocoagulation or vitrectomy.

The rates of disease progression reported at four years by the different study groups were as follows:

Conditions	Intensive therapy (%)	Standard therapy (%)	Adjusted odds ratio	95% Confidence interval	P value
Hyperglycemia	7.3	10.4	0.67	0.51–0.87	0.003
Hypertension	10.4	8.8	1.23	0.84–1.79	0.29
Dyslipidemia	6.5	10.2	0.60	0.42–0.87	0.006

Based on the study findings, it was concluded that intensive combination treatment for dyslipidemia and intensive glycemic control could be promising in reducing the rate of diabetic retinopathy progression, but not intensive blood pressure therapy.

An earlier review by Rodriguez-Fontal et al (*Current Diabetes Reviews*, 2009) reported the significance of intensive glycemic control in reducing the risk of diabetic retinopathy by 27%. The researchers also reiterated the need for initiating the intensive therapy early, during the clinical course of diabetes.

According to 2007 statistics published by the National Diabetes Information Clearinghouse (NDIC), diabetic retinopathy is the principal cause for 12,000 to 24,000 new cases of blindness, annually in the US. Symptoms of this diabetes-linked complication include ocular hemorrhage, macular edema, and blurred vision, which causes difficulty in reading and driving.

An earlier review by El-Asrar et al (*Current Opinion in Ophthalmology*, 2009) reported intensive regulation of blood pressure, tight metabolic control, laser photocoagulation, and vitrectomy as the standard therapeutic interventions for diabetic retinopathy. The researchers also validated the need for conducting more randomized controlled clinical trials to evaluate the efficacy of emerging treatment modalities, including islet cell transplantation, ruboxistaurin, intravitreal hyaluronidase, and fenofibrate, as mono/combination therapies in the management of diabetic retinopathy. ■

References available online at [www.medinewsdirect.com](http://www.medinewsdirect.com)

## Study Suggests Allopurinol may be Safe and Effective Against Ischemia

Allopurinol, the prototype xanthine oxidase inhibitor, has been indicated for the management of gout and other conditions associated with hyperuricemia for more than half a century. Recent reports have suggested the probable role of xanthine oxidase in ischemic injuries, thereby prompting researchers to consider allopurinol as a treatment option. Now, a recent double-blind, randomized, placebo-controlled, crossover study, published in the latest issue of *The Lancet*, reports the potential use of the drug in treating chronic stable angina.

Allan D Struthers, Professor of Cardiovascular Medicine, Centre for Cardiovascular & Lung Biology, University of Dundee, UK, and colleagues recruited 65 patients into the study conducted at a hospital and two infirmaries. The inclusion criteria were chronic stable angina for a minimum of two months, a positive exercise tolerance test, and angiographically proven coronary artery disease. Based on computer-generated randomization, the patients were allocated to allopurinol or placebo group for 6 weeks prior to crossover. The primary outcome measure was time to ST depression, and the secondary outcome measures were time for developing chest pain and total exercise time.

During the first treatment period, 28 and 32 patients were analyzed out of the 31 and 34 assigned to the allopurinol, and placebo groups respectively. During the second treatment period, 60 patients were analyzed. The outcome measures recorded are shown in the table below.

Outcome measure	Baseline (seconds)	Allopurinol (seconds)	Placebo (seconds)	P value	Point estimate * (seconds)
Median time to ST depression	232	298	249	0.0002	43
Time to angina	234	304	272	0.001	38
Median total exercise time	301	393	307	0.0003	58

\* Absolute difference between allopurinol and placebo

The results show that patients on allopurinol were able to exercise for 25% longer before the onset of angina or had ST depression, compared to placebo. There were no adverse effects reported with the drug. It should be noted that although the sample size was small, the P values and the size of the effects were significant.

As per the American Heart Association statistics, 10.2 million Americans are estimated to experience angina in the year 2010. Stable angina is a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arms, typically elicited by exertion or emotional stress, and relieved by rest or nitroglycerin. Patients responding poorly to nitroglycerin invariably require revascularization procedures such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Now, with the current study suggesting positive outcomes with allopurinol, the xanthine oxidase inhibitor may prove to be an inexpensive, effective, well-tolerated and a safe, treatment option in such patients. ■

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## Simple Blood Test Could Help Predict Age at Menopause

A recent breakthrough study reports the development of a blood test that helps predict the approximate age at which a woman would attain menopause. The findings of this population-based cohort study were presented at the 26th annual meeting of the European Society of Human Reproduction and Embryology (ESHRE) held at Rome from 27th to 30th June 2010. The researchers are hopeful that the test could help women determine the age at which they reach menopause and accordingly plan their motherhood.

In order to determine the menopausal age, Fahimeh Ramezani Tehrani, president of the Reproductive Endocrinology Department, Endocrine Research Centre, Iran, and co-workers, analyzed anti-Mullerian hormone (AMH) concentrations in blood samples of 266 women, aged between 20 and 49 years. The blood samples were again collected twice, at three-year intervals, and details regarding the patients' reproductive history and socioeconomic background gathered. In addition to this, the subjects underwent physical examination every three years.

A statistical model was developed to assess the menopausal age from a single analysis of serum AMH levels. Based on this model, the subjects' mean age at menopause was evaluated by measuring varying serum AMH levels at different phases of reproductive life. The following results were documented during the study:

Subject age (years)	AMH levels (ng/mL)	Estimated age at menopause
20	≤4.1	<45 years
25	3.3	
30	2.4	
20	4.5	>50 years
25	3.8	
30	2.9	

The menopausal age calculated through this model was in line with the actual menopausal age for 63 subjects who attained menopause during the study period. The mean difference between the predicted and actual age at menopause was reported to be only a third of a year, and the highest margin of error was 3 to 4 years. It was also noted that the average age at menopause in the subjects was around 52 years.

Based on these findings, the researchers concluded that AMH levels could serve as a predictive factor in identifying a woman's reproductive status more practically than chronological age independently.

A similar study by van Rooij, et al (*Menopause*, 2004) reported that AMH alone, or in combination with inhibin B, are promising predictors for the occurrence of menopausal transition. They also noted that inhibin B enhanced the prediction.

Antral follicle count (AFC) is one of the common predictors of the female reproductive status as it is associated with age at menopause, and birth of the last offspring. However, only low counts present clinically practical estimation of the reproductive status and may vary from cycle to cycle. Serum antimüllerian hormone levels, being highly correlated with the antral follicle count, independent of menstrual cycle, and easily measurable, could make a useful indicator of menopausal age. ■

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## Use of Psychotropics During Pregnancy may Increase Risk of Birth Defects

A recent study by Danish researchers has reported that the intake of psychotropic medications could pose serious adverse effects during pregnancy, including the possibility of birth defects in the offspring. The findings of the study are published in the recent issue of the open access journal *BMC Research Notes*.

Professors Lise Aagaard and Ebba Holme Hansen from the University of Copenhagen, investigated adverse effects of such drugs during gestation by analyzing adverse drug reaction (ADR) reports of children documented in the Danish Medicines Agency (DKMA). The study assessed the severity, type, and distribution of ADRs annually (during 1998 and 2007), along with age/gender of 2,437 children (ranging from new borns to 17 years of age) and suspected medication.

The key study findings were as follows:

- Of the total 4,500 ADRs recorded, 429 were due to psychotropic medications
- Of the psychotropic ADRs, 56% were found to be serious and included neonatal withdrawal syndrome, premature labor, and birth deformities like ventricular septal defects
- Approximately 20% of the psychotropic medication-associated ADRs were noted in children  $\leq 2$  years and one-half of them in adolescents (11-17 years)
- About 60% of the ADRs were reported in boys
- Of all ADRs, 40% were related to nervous and psychiatric disorders
- Many serious ADRs, like those seen in children  $\leq 2$  years, were assumed to be due to the maternal use of psychotropic drugs such as antipsychotics and antidepressants during pregnancy
- Occurrence of the ADRs was found to be 42% for psychostimulants, and 31% and 24% for antidepressants and antipsychotics, respectively

The researchers concluded that the findings serve as a caution to the medical and healthcare community, and thereby recommended offering greater care in prescribing psychotropic drugs to pregnant women.

A recent review by Menon (*Archives of Gynecology and Obstetrics*, 2008) reported that pregnancy could considerably affect drug levels in plasma. Additionally, immature fetal and neonatal physiology could make the offspring more susceptible to the adverse effects of pharmacological agents, thereby raising the risk for long-term behavioral problems, teratogenicity, and perinatal syndromes.

While untreated mental illness holds a range of repercussions on pregnancy outcomes and the child well-being, it is crucial for the physicians to perform an individualized risk-benefit analysis prior to prescribing the psychotropic medications, especially during pregnancy. Careful psychiatric monitoring and corresponding multidisciplinary care by the physicians could help optimize the complex management of psychiatric illnesses in pregnant women. ■

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## Botox Treatment Linked to Limited Emotional Experience

Several studies have validated the safety, tolerability, and efficacy profiles of botulinum toxin injection (Botox) for various therapeutic as well as esthetic indications. In contrast to these findings, a recent study published in the journal *Emotion* reports that the injection may adversely affect the emotional experience of the treated subjects.

Joshua Ian Davis, Term Assistant Professor, Department of Psychology, Barnard College of Columbia University, New York, and coworkers, tested the facial feedback hypothesis (FFH), which states that the emotional experience is subjective to the feedback from facial expressions. During the follow-up, the researchers compared the self-reported emotional experience between Botox-treated patients and the control group administered with restylane injection, a U.S. Food and Drug Administration (FDA)-approved cosmetic filler not affecting facial muscles.

Analysis of the patients' response to positive and negative video-clips showed that there was no change in emotional responses before and after the treatment with Botox. However, a substantial reduction in strength of emotional experience was noted in the Botox group as opposed to the controls. The key study findings were based on the following observations:

- Decrease in response to mildly positive clips among Botox patients after the treatment
- Unanticipated increase in response in the control group upon watching negative clips

The study concluded that facial expressions, although not a major factor, may affect the emotional experience.

In view of reports on the occurrence of adverse events

with Botox, the FDA conducted a safety review of the drug and requested the manufacturing companies to provide a boxed warning for the following four botulinum toxin drug products.

- Botox (onabotulinumtoxinA | Allergan Inc.)
- Botox Cosmetic (onabotulinumtoxinA | Allergan Inc.)
- Myobloc® (rimabotulinumtoxinB | Solstice Neurosciences)
- Dysport™ (abobotulinumtoxinA | Ipsen)

The boxed warning cautions about the chances of spreading the effects of the botulinum toxin from injection site to other parts of the body, which can cause symptoms similar to botulism, such as difficulty in breathing and swallowing, and even death. However, the dermatologic use of the toxin for the following indications at recommended doses is not associated with any serious adverse effects:

- Frown lines between the eyebrows
- Severe underarm sweating
- Eyelid twitches
- Crossed eyes

In view of the recent study findings, further studies are mandatory to clearly elucidate the enhanced risk for emotional consequences linked to Botox injections. ■

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