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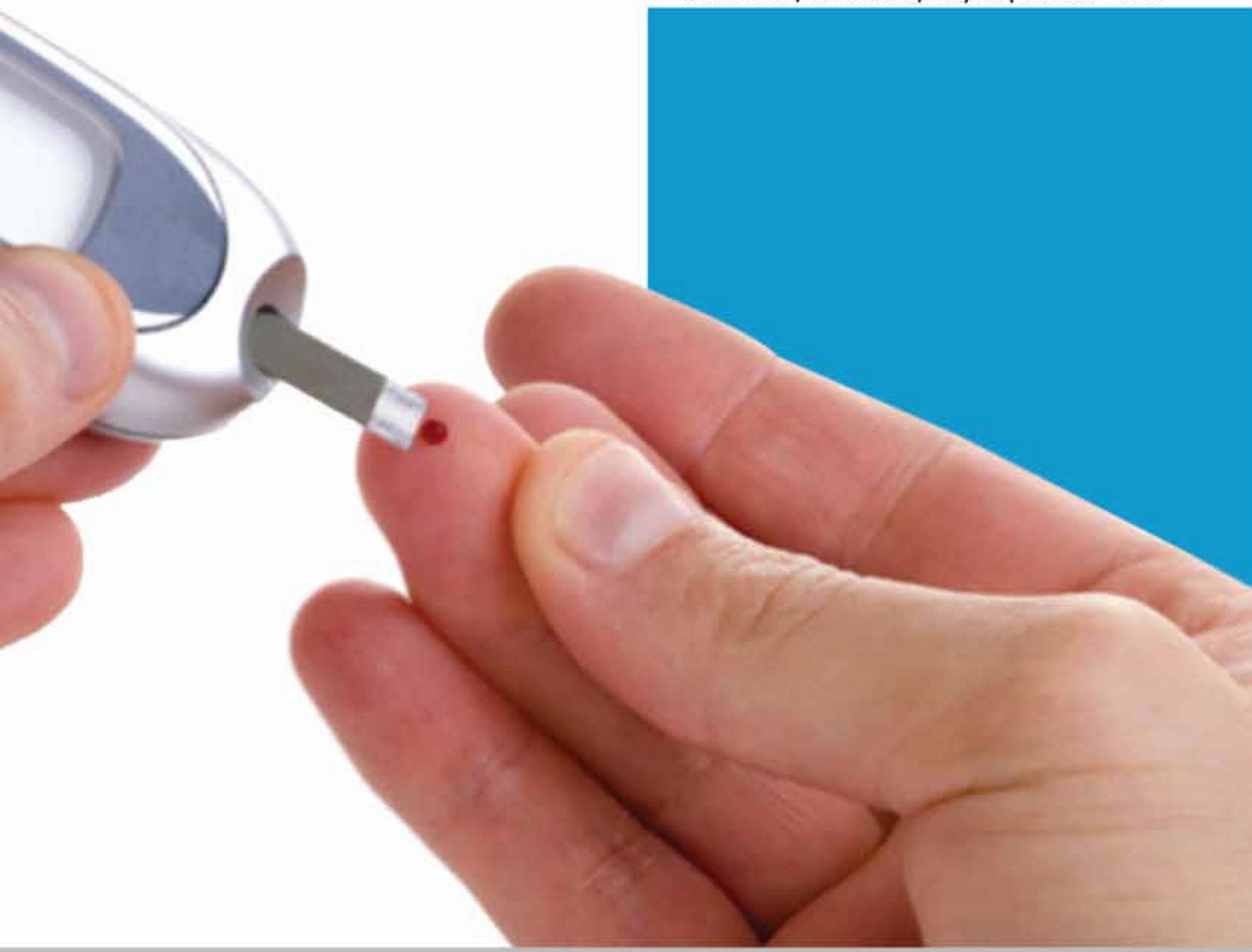

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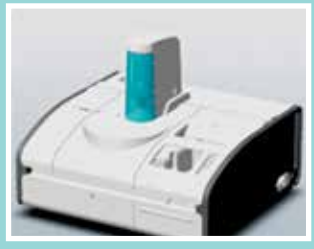

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Moderate Calorie Restriction and Exercise may Improve Heart Health in Obese Older Adults

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Immediate Past President, Endocrine Society of India

Results of a latest study show that combining aerobic exercise with a moderate reduction in total daily calories up to 200 calories daily resulted in greater improvements in aortic stiffness when compared to exercise alone or exercise plus a more restrictive diet in older adults with obesity.

The study published August 2 in the journal Circulation analyzed the effects of exercise with or without high caloric restriction on proximal aortic stiffness in 160 older adults, aged 65-79 years, with obesity (BMI 30-45 kg/m2). The participants were randomized into one of three study groups: aerobic exercise only, aerobic exercise with a regular diet, aerobic exercise + moderate caloric restriction (reduction of ~250 calories) or aerobic exercise + more intensive caloric restriction (reduction of~600 calories) for 20 weeks. Aortic structure and function were assessed by cardiac MRI to measure aortic arch pulse wave velocity and distensibility. Higher pulse wave velocity and lower distensibility are indicative of aortic stiffness.

The results showed that over the 20 weeks of the intervention, weight loss in the aerobic exercise + moderate caloric restriction (-8.0 kg) and aerobic exercise + more intensive caloric restriction (-8.98 kg) groups was significantly greater compared to the exercise alone group (-1.66 kg). This weight loss was found to be associated with significant improvement in aortic stiffness only in the participants in the aerobic exercise + moderate caloric restriction group. A 21% increase in distensibility and an 8% decrease in pulse wave velocity were observed in this group. No significant change in the aortic stiffness measures were observed in the exercise-only group or the exercise + more intensive calorie restriction group.

The BMI, total fat mass, percent body fat, abdominal fat and waist circumference showed an improvement in both calorie-restricted groups compared to the exercise-only group. Another interesting observation was that the weight loss was similar between the calorie-restricted groups despite nearly two times fewer calories (26.7% reduction in calories vs. a 14.2% reduction in calories) in the more intensive calorie restriction group. But participants in the more intensive calorie restriction group did not show any improvement in aortic stiffness.

These results show that calorie restriction alone does not help and a strict calorie restriction may not be actually required. Adding exercise augments the cardiac beneficial effects of calorie restriction as well as weight loss and distribution of body fat. In addition, it also prevents or delays the onset of diabetes and other obesity-related conditions.

Hence, moderate calorie restriction along with regular exercise will help to obtain maximum beneficial effects on vascular health and reduce associated morbidity and mortality.

(Source: Brinkley TE, et al. Effects of exercise and weight loss on proximal aortic stiffness in older adults with obesity. Circulation. 2021;144(9):684-96.)

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REVIEW ARTICLE

Reversing Type 2 Diabetes Through Functional Medicine

PRITI NANDA SIBAL

ABSTRACT

Diabetes is one of the biggest global health emergencies of the 21st century. Overall, 425 million people worldwide are estimated to have diabetes, with India being home to the second largest number of people suffering with diabetes. A recent analysis showed that diabetes-related complications are continuously on the rise. These complications affect almost all systems of the body leading to retinopathy, neuropathy, nephropathy, cardiovascular disorders, diabetic foot, depression, anxiety and even eating disorders in diabetes patients, severely affecting the patient's quality-of-life. Traditional approach towards treating type 2 diabetes does not try to alter the course of diabetes at the prediabetes stage. It works on the symptoms, and as a result, the basic pathology keeps on getting intense and therefore, the number and dose of medicine keeps on increasing every few years. Functional medicine provides a holistic approach towards managing diabetes and reducing the complications associated with it. This review discusses the functional medicine approach, detailing the early diagnosis approach, preventive strategy, regular monitoring of blood glucose parameters and treatment approach of diabetes including diet management, exercise, functional foods, nutritional supplements and genetic and lifestyle interaction.

Keywords: Functional medicine, diabetes, reverse diabetes, diet, stress, exercise, nutritional medicine, functional foods

Diabetes is one of the largest global health emergencies of 21st century. Overall, 425 million people worldwide are estimated to have diabetes, with almost 79% living in low- and middle-income countries. India is home to the second largest number of adults living with diabetes worldwide, after China. In 2014, 8.5% of adults aged 18 years and older had diabetes. In 2016, diabetes was the direct cause of 1.6 million deaths and in 2012 high blood glucose was the cause of another 2.2 million deaths.

Diabetes is an ever-growing problem, primarily due to a lack of lifestyle education and physical activity as well as the consumption of high-calorie, low-nutrient, processed foods. Diabetes has various and often devastating complications such as heart disease, stroke, high blood pressure, nerve damage, kidney damage, eye damage, foot damage, hearing impairment, skin conditions such as bacterial and fungal infections and even Alzheimer's disease. With 1 out of 11 people suffering from diabetes, the disease disrupts all aspects of human physiology and increases the risk of cardiovascular disease, cancer, cognitive decline and virtually every other disease.

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Functional medicine plays a crucial role in managing and reversing diabetes by applying itself to laboratory testing, performing an extensive evaluation of the patients' overall lifestyle and health history leading to detection of issues, which can be reversed using intensive lifestyle changes. Functional medicine can control the blood glucose levels, as well as help in reducing many other linked health issues of the patient. Functional medicine is successful in not only optimizing glycosylated hemoglobin (HbA1c) and blood glucose levels, but also reversing diabetes completely.

CONVENTIONAL MEDICINE APPROACH

In conventional approach to diabetes treatment, inadequate time is spent on identifying the root cause of the disease. In traditional practice, the common approach is to wait till the patient is in later stages of diabetes and not much is done to alter the course of the disease in its early (insulin resistance) or prediabetes stage when the body is more responsive to diet and lifestyle changes.

FUNCTIONAL MEDICINE APPROACH TOWARDS DIABETES

Functional medicine approach works by applying itself to detailed laboratory testing, performing an extensive evaluation of the patient's overall lifestyle and health history leading to detection of issues, which can be

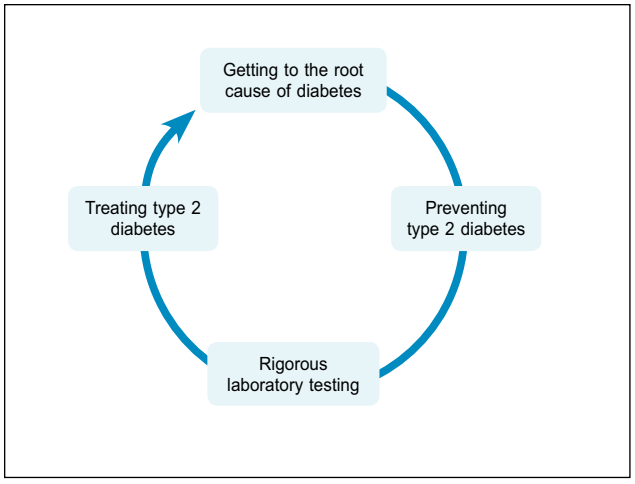

Figure 1. Functional medicine approach for diabetes management.

reversed using intensive lifestyle changes. In patients who are already diagnosed with type 2 diabetes, functional medicine approach tends to look for the root cause and correct it, thereby alleviating many (if not all) symptoms associated with diabetes (Fig. 1).

Getting to the Root Cause of Diabetes

Blood glucose is a symptom of diabetes and not the cause of diabetes. Hence, it is important to understand that treating only the symptoms will not be helpful in alleviating diabetes. It thus becomes imperative to detect the primary cause of diabetes.

Insulin resistance

Insulin is an important hormone released by β-cells in the pancreas with one of its key functions being balancing the blood glucose levels in the body. To achieve blood glycemic control, insulin undergoes a process which allows the glucose floating in the blood to efficiently get absorbed into individual cells throughout the body (muscle, fat, liver, etc.). In the presence of insulin resistance, this process is disrupted, leading to a release of more insulin, to ensure that the glucose is absorbed in the body cells. However, as the blood glucose increases owing to lifestyle, genetics, toxins or mitochondrial function impairment, the β-cells are unable to produce more insulin, which causes an excess build-up of glucose in the blood. This excess glucose then damages cells throughout the body, and these symptoms present as diabetes complications in the body.

Chronic stress

Chronic stress is another factor leading to insulin resistance which in turn causes type 2 diabetes. Stress increases cortisol levels in the body, which increases blood glucose levels. In case, the stress is temporary, there is no problem; however, if the stress persists due to a high-stress work environment, or disturbed family life, then the persistently elevated cortisol causes persistently elevated blood glucose and the β-cells are unable to secrete adequate insulin. High perceived stress is associated with insulin resistance and a significantly increased risk of type 2 diabetes in adults.

Lack of sleep

Research has shown that sleep deprivation is also linked to insulin resistance. A study conducted among 9 healthy subjects (5 men and 4 women) has shown that partial sleep deprivation during only a single night induces insulin resistance in multiple metabolic pathways in healthy subjects. This physiological observation is of relevance for variations in glucose regulation in patients with type 2 diabetes. Sleep deprivation increased plasma nonesterified fatty acid levels.

Microbiome

Another theory suggests that an imbalance in the body's flora and fauna leads to an overgrowth of harmful bacteria carrying lipopolysaccharide. Lipopolysaccharide release has also been associated with insulin resistance. Research has also shown that patients with hypovitaminosis D are at higher risk of insulin resistance and the metabolic syndrome.

Methylation status

Epigenetic modifications, including DNA methylation, have been identified as one mechanism by which the environment interacts with the genome and there is evidence that alterations in DNA methylation may contribute to the increased prevalence of type 2 diabetes.

Smoking

Cigarette smoking is a well-known risk factor in many diseases, including diabetes. Many studies have reported the unfavorable effects of smoking on diabetes mellitus. Smoking increases the risk of developing diabetes, and aggravates the micro- and macrovascular complications of diabetes mellitus. Smoking is associated with insulin resistance, inflammation and dyslipidemia, but the exact mechanisms through which smoking influences diabetes mellitus are not clear. However, smoking cessation is one of the important targets for diabetes control and the prevention of diabetes complications.

Genetic propensity to diabetes

Type 2 diabetes has a strong link to family history and lineage, although it also depends on environmental

factors. The underlying genetic basis for mortality likely involves complex interactions with factors related to ethnicity, type 2 diabetes and body weight. Type 2 diabetes is partly genetically determined. Genetic factors that increase type 2 diabetes susceptibility may also raise mortality risk through type 2 diabetes or its related complications.

Preventing Type 2 Diabetes

Functional medicine takes a proactive approach in preventing type 2 diabetes. A detailed testing allows functional medicine practitioners to identify and initiate the reversal of problematic changes such as insulin resistance much sooner than the standard care in conventional approach of diabetes management. Functional medicine has laid down completely new standards for allowing early detection of diabetes so that it can be easily nipped in the bud.

Detailed Laboratory Testing

Functional medicine follows a detailed lab testing and has more sensitive parameters than other conventional diagnostic methods. It is a well-known fact that conventional lab ranges for blood glucose and HbA1c which are considered by clinicians when screening for diabetes allow for quite high range of blood sugars before diabetes is diagnosed.

Current recommendations from the American Diabetes Association for laboratory values that qualify a patient for type 2 diabetes include:

- HbA1c: <7.0%
- Two-hour postprandial blood glucose: <180 mg/dL
- Fasting blood glucose: 80-130 mg/dL.

However, functional medicine looks for early warning signs such as mild elevations of glucose or of insulin resistance. Early markers for type 2 diabetes and related conditions in functional medicine are:

- Fasting glucose: 84 mg/dL
- Elevated triglyceride level
- Elevated uric acid level
- Low high-density lipoprotein (HDL)
- Elevated low-density lipoprotein (LDL)
- HbA1c: >5.4%
- Increased insulin or C-peptide levels (for long-term average insulin production)
- Antibodies such as glutamic acid decarboxylase (GAD65), pancreatic islet cells
- Increased waist size (>40 inches in men; >35 inches in women)
- Waist-to-hip ratio >0.85 in females and >0.90 in males
- Elevated blood pressure.

All these early warning signals, help in early diagnosis of diabetes or insulin resistance, hence curbing the progression to diabetes. Timely approach targeting the cause of this variation helps in completely reversing the condition and helps patients in regaining optimal health conditions.

Treatment of Type 2 Diabetes

In contrast to conventional medicine approach, functional medicine takes the path of supporting diet and lifestyle changes in the patient as the primary treatment for type 2 diabetes (Fig. 2) and optimizing the laboratory markers.

Under the vestiges of functional medicine, the patient is educated at length about food and nutrition, lifestyle changes and balancing laboratory markers through various scientific approaches, a typical visit averaging about between half an hour to 90 minutes.

Healthy gut

Research has shown that an altered, inflammatory gut microbiota is of utmost importance in the development of type 2 diabetes. A recent study showed that metformin has an effect on the gut microbiota; the drug increases levels of *Akkermansia muciniphila*, which is a commensal gut bacterium, associated with reduced inflammation and improved metabolic health. This supports the fact that the gut microbiota plays a pivotal role in type 2 diabetes.

Several prebiotics and probiotics have been investigated for their antidiabetic and gut health-promoting effect. A prebiotic fiber found in mushrooms and konjac root has been found to boost the blood glucose levels,

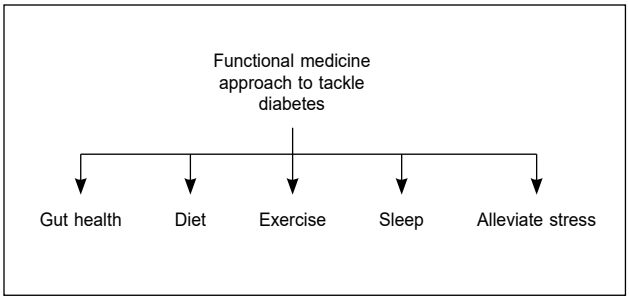

Figure 2. Components of functional medicine approach to manage diabetes.

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reducing effects of metformin. Similarly, inulin, a prebiotic found naturally in chicory, garlic, onions, leeks and asparagus, reduces fasting blood glucose and promotes a more metabolically healthy gut microbiota. Certain probiotic strains such as Lactobacilli and Bifidobacterium also improve biomarkers of inflammation and oxidative stress in type 2 diabetes and lower fasting blood glucose by promoting an anti-inflammatory gut microbiota.

Diet

Low-carbohydrate diet

A persistently growing body of research has indicated that low-carbohydrate diets are superior to high-carbohydrate diets for the treatment of type 2 diabetes. A recent systematic review and meta-analysis of 18 randomized controlled trials has found that reducing dietary carbohydrates produces significant-improvements in HbA1c, triglycerides and cholesterol, while also lowering patient's diabetes medication requirements.

Various large-scale clinical studies have compared the effectiveness of low-carbohydrate diet with high-carbohydrate diet to treat diabetes. The results of these studies have again reiterated that low-carbohydrate diets consistently outperform high-carbohydrate diets for the management of type 2 diabetes. In addition, it also produces more significant improvements in blood glucose stability and lipid profiles and significantly reduces the need for medications. Along with quantity, it is also important to refine the quality of carbohydrates being consumed by the patients.

Low glycemic index diet

A meta-analysis of six small studies (n = 202) with short duration, revealed that overweight or obese people on low glycemic index diets lost more weight and had better improvement in lipid profiles than those receiving other diets.

Cyclic ketogenic diet

Cyclic ketogenic diet has emerged as an effective alternative diet that relies less on medication, and may even be a preferable option when medications are not available. This form of keto diet helps patients follow it more consistently and reap best and long-term results. The ketogenic diet substantially reduces the glycemic response that results from dietary carbohydrate as well as improves the underlying insulin resistance. Results of a study demonstrated that low-carbohydrate, keto diet resulted in significant improvement of glycemia, as measured by fasting glucose and HbA1c in patients with type 2 diabetes. An important point to note here is that this improvement was observed while diabetes medications were reduced or even discontinued. Along with this, participants also experienced moderate reductions in body weight, waist circumference and percent body fat. Another study has also shown that Mediterranean diet was associated with better glycemic control and cardiovascular risk factors than control diets, including a lower fat diet, suggesting that it is suitable for the overall management of type 2 diabetes.

Mediterranean diet

In a randomized, single-blind controlled trial, it was shown that a Mediterranean-style diet might be effective in reducing the prevalence of the metabolic syndrome.

Nutraceuticals in insulin resistance syndrome

Nutraceuticals or functional foods such as plant proteins have been shown to improve insulin resistance and reduce triglyceride secretion. Pro- and prebiotics, that are able to modify intestinal microbiome, reduce absorption of specific nutrients and improve the metabolic handling of energy rich foods. Lastly, specific nutraceuticals have proven to be of benefit such as red-yeast rice, berberine, curcumin, acai, berry antioxidants, *Ginkgo biloba*, green tea as well as vitamin D. All these can improve lipid handling by the liver as well as ameliorate insulin resistance.

Micronutrients

Micronutrient recommendations for a diabetes patient include chromium, vitamin D, magnesium, CoQ10 and alpha-lipoic acid. Alpha-lipoic acid has been shown to be beneficial in the treatment of peripheral diabetic neuropathy. Benefits of magnesium supplementation on metabolic profile in diabetes patients have been found in many clinical studies.

Exercise

It is a well-known fact that a sedentary lifestyle is a significant risk factor for type 2 diabetes, so exercise should be a central part of any treatment plan for the disease. Research has indicated that walking for just 30 minutes a day reduces the risk of type 2 diabetes by approximately 50%. High intensity interval training also appears beneficial as it reduces fasting blood sugar, HbA1c and cardiovascular complications in type 2 diabetes and is more effective than continuous aerobic activity for improving blood sugar control.

In addition to increased exercise, reducing sedentary time in daily life is also essential. Alternate sitting with working at a standing desk or treadmill desk, breaking

up prolonged sitting with standing or walking has been shown to improve the post-meal blood glucose response in those at risk for diabetes.

Maintaining sleep hygiene

Research has shown that short sleep duration or sleep loss may promote type 2 diabetes by interfering with energy metabolism and increasing insulin sensitivity. Sleep loss also impairs satiety, triggering cravings and overconsumption of sugary processed foods that increase the risk of diabetes. Obstructive sleep apnea, a common cause of sleep loss, promotes type 2 diabetes by inducing hypoxia, which in turn impairs insulin production by pancreatic β-cells.

Functional medicine focusses on strategies that correct obstructive sleep apnea, reduces severity of apnea and improves sleep quality and duration.

Stress management

Research has shown that reducing psychological stress can improve blood sugar management in type 2 diabetes. Functional medicine adopts an approach to alleviate patient's chronic stress and improve his overall health as well as reverse diabetes condition. Meditation, yoga, laughter therapy and breathing exercises have been found to reduce fasting blood glucose and post-meal glucose hike in diabetes patients. Functional medicine practitioners offer guided meditation, breathing exercises and relaxation techniques to the patients to alleviate stress.

Pharmacological management

Although currently there are no Food and Drug Administration (FDA) approved medications specifically for the treatment of insulin resistance, the pharmacological agents that are often prescribed for insulin resistance in some patients include metformin and thiazolidinediones. Insulin is also used for some cases of insulin resistance. Metformin is a biguanide insulin sensitizer that is used as a first-line drug.

CONCLUSION

Poor diet, a sedentary lifestyle, inadequate sleep, chronic stress, gut dysfunction and environmental toxins, genetics, toxic thoughts and disturbed mitochondrial function play a significant role in causing diabetes. Functional medicine is a science-based approach to preventing and treating diabetes that is focused on diet and lifestyle changes, and is the most effective first-line strategy for managing type 2 diabetes. It is an effective way to prevent, treat and manage type 2 diabetes. Reversing type 2 diabetes is no more a dream now.

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■■■■

CLINICAL STUDY

Posology of Antidiabetic Drugs and Insulins: A Review of Standard Textbooks

GARIMA BHUTANI*, SANJAY KALRA†

ABSTRACT

Objectives: The aim of this bibliographic review is to assess whether standard pharmacology, endocrinology and diabetology textbooks adequately mention the details regarding timings of administration, frequency and dose of various oral and injectable antidiabetic drugs. **Material and methods:** Four standard textbooks of pharmacology, two of diabetology and three of endocrinology were assessed for the published information regarding dose, timing and frequency of antidiabetic drugs. **Results:** Various omissions and contraindications were found in the coverage of glucose-lowering drugs in standard textbooks. Proper timing and frequency of administration of sulfonylureas, thiazolidinediones, SGLT2 inhibitors, GLP receptor agonists and DPP-4 inhibitors have been omitted in majority of the textbooks. **Conclusions:** This article stresses upon the need of a uniform source of information for providing adequate and standardized knowledge regarding timing, frequency and dose of antidiabetic drugs.

Keywords: Posology, antidiabetic drugs, postprandial hyperglycemia

Correct timing of glucose-lowering therapy is an important aspect of diabetes pharmacotherapeutics. Matching the dose of a particular drug with meals depends upon its mechanism of action and pharmacokinetic profile. This timing varies from class-to-class and drug-to-drug. Each drug has a specific time action profile. This should match with food absorption. Inappropriate timing/frequency/dose of administration may lead to unwanted hyperglycemia or hypoglycemia leading onto poor glycemic control or complications in the patients.

This glycemic variability is easily avoidable with the better knowledge and understanding of appropriate dose, timing of administration and frequency of drug administration. Pharmacology, diabetology and endocrinology textbooks are an important and reliable source of such information, both for students and clinicians. This article aims at assessing the adequacy of the knowledge provided by these textbooks regarding posology (i.e., dose, frequency and timing of antidiabetic drugs).

MATERIAL AND METHODS

Some of the most popular and most commonly read textbooks of pharmacology, diabetology and endocrinology were included in the study. Four standard textbooks of pharmacology (2 by Indian authors and 2 by US authors) were analyzed. Two textbooks of diabetology were also studied, out of which 1 textbook is by Indian author and other is by US author. Three textbooks of endocrinology (2 US and 1 Indian in origin) were also assessed for the desired information. Latest available editions of the textbooks were taken for analysis.

RESULTS

The results of the analysis have been tabulated in Table 1, which shows the comparison of information about antidiabetic drugs available in different textbooks.

DISCUSSION

This bibliometric analysis highlights various omissions and contraindications in the coverage of glucose-lowering drugs in standard textbooks.

Metformin is covered well by 8 out of 9 textbooks, with 6 of them mentioning relatively concordant doses, and

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Table 1. Comparison of Information in Pharmacology, Endocrinology and Diabetology Textbooks

Drug class	Drug	Goodman and Gilman's the Pharmaceutical Basis of Therapeutics[1]	Basic and Clinical Pharmacology[2]	Essentials of Medical Pharmacology[3]	Principles of Pharmacology[4]	Endocrinology[5]	Textbook of Diabetes[6,7]	RSSDI Text book of Diabetes Mellitus[8-10]	Manual of Clinical Endocrinology[11]	Williams Textbook of Endocrinology[12]
Biguanides	Metformin	0.5-2.5 g b.i.d., with meals	500 mg-2.55 g at bedtime for fasting hyperglycemia and before meals for postprandial hyperglycemia	0.5-2.5 mg, 1-2 doses per day	500 mg before breakfast and 500 mg with evening meal	Start with 500 mg o.d. Titrate up to 500-1,000 g b.i.d., given with meals	500 mg o.d.- 2,550 mg (divided doses) with meals or immediately before meals[6]	-	500 mg o.d. to 2,500 mg in divided doses	At least b.i.d.
	Metformin SR	Max dose is 2 g o.d., with meals	-	-`	-	With evening meal	Once-daily in morning or b.i.d. (morning and evening)[6]	-	-	-
Thiazolidinediones	Pioglitazone	15-45 mg o.d.	15-45 mg o.d.	15-45 mg o.d.	11-45 mg o.d.	15-45 mg daily	15-45 mg/day[6]	-	15-45 mg/day o.d.	-
	Rosiglitazone	4-8 mg o.d.	2-8 mg o.d. or b.i.d.	-	4-8 mg o.d.	2-8 mg daily	4-8 mg[6]	-	-	-
Meglitinide analog	Repaglinide	0.5-16 mg preprandially	0.25-4 mg, just before each meal (max 16 mg/day)	1-8 mg, 3-4 doses/day, before each major meal	0.25-4 mg shortly before each meal	0.5-2 mg t.i.d. with each meal	0.5-4 mg, 15-30 min before each main meal[6]	0.5-4 mg in 3-4 doses, just before or soon after starting a meal[8]	Preprandial dosing	Max 4 mg with each meal
	Nateglinide	180-360 mg, 1-10 min before a meal	60-120 mg, just before meals	180-480 mg, 3-4 doses per day, 10 min before meal	60-120 mg, shortly before each meal	60-120 mg t.i.d. with each meal	60-180 mg t.d.s., preprandial use[6]	60-180 mg in 3-4 doses, just before or soon after starting a meal[8]	Preprandial dosing	120 mg with each meal

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Sulfonylureas	Glipizide	5-40 mg o.d. or b.i.d.	5-30 mg, 30 min before breakfast	5-20 mg, o.d. or b.i.d.	5-20 mg o.d. or b.i.d.	2.5-5 mg initially. Max 40 mg divided b.i.d.	2.5-20 mg[6]	1.25-15 mg in 2-3 doses, 20-30 min before meals[8]	5-40 mg/day	Initial 5 mg, Max 40 mg, divided b.i.d.
	Glipizide extended release	5-20 mg daily	Once-daily morning dose, max 20 mg/day	-	-	2.5-5 mg initially. 20 mg o.d. max dose	Once-daily dose[6]	-	5-20 mg/day	Initial 5 mg. Max 20 mg o.d.
	Gliclazide	-	-	40-240 mg, o.d. or b.i.d.	40-250 mg o.d. or b.i.d.	-	40-320 mg[6]	40-240 mg in 1-3 doses, 20-30 min before meals[8]	-	-
	Gliclazide MR	-	-	-	-	-	30-120 mg o.d.[6]	-	-	-
	Glyburide (glibenclamide)	1.25-20 mg o.d. or b.i.d.	1.25-20 mg, single morning dose	2.5-15 mg o.d. or b.i.d.	5-15 mg o.d. or b.i.d.	1.25-5 mg initially. Max dose 20 mg, divided b.i.d.	1.25- 15 mg[6]	1.25-20 mg in 1-3 doses/ day, 20-30 min before meals[8]	1.25-20 mg/day	Initial dose 2.5 mg. Max dose 20 mg, divided b.i.d.
	Micronized glyburide	0.75-12 mg daily	-	-	-	1.5-3 mg initial dose. Max dose is 6 mg, b.i.d.	-	-	0.75-12 mg/day	Initial 3 mg. Max 6 mg b.i.d.
	Glimepiride	1-8 mg o.d.	1-8 mg o.d.	1-6 mg o.d. or b.i.d.	1-6 mg o.d.	1-2 mg initially. Maximum dose is 8 mg o.d.	1-6 mg[6]	1-8 mg o.d., 20-30 min before meals[8]	1-8 mg/day	1-8 mg o.d.
α-Glucosidase inhibitors	Acarbose	25-100 mg, before meals	25-100 mg, just before ingesting the final portion of each meal	50-100 mg t.d.s., at the beginning of each major meal	50-100 mg t.d.s. at the beginning of each major meal	25-100 mg t.i.d. with first bite of carbohydrate containing meal	50 mg o.d. to 200 mg t.d.s., with meals[6]	25 mg t.d.s. at the start of each main meal to max of 100 mg t.d.s.[9]	-	-

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	Voglibose	-	-	200-300 mg t.d.s. just before meals	-	-	With meals[6]	0.2 mg t.d.s., just before each meal - max of 0.3 mg t.d.s.[9]	-	-
	Miglitol	25-100 mg before meals	25-100 mg just before ingesting the final portion of each meal	25-100 mg t.d.s. at the beginning of each major meal	-	25-100 mg t.i.d. with first bite of carbohydrate containing meal	With meals[6]	-	-	-
DPP-4 inhibitors	Vildagliptin	50-100 mg daily	-	50-100 mg o.d. or b.i.d.	50 mg o.d. before meals	-	50 mg b.i.d.[6]	50 mg o.d. or b.i.d., with or without food[10]	50 mg b.i.d.	-
	Linagliptin	-	-	-	-	-	-	-	5 mg/day	-
	Sitagliptin	100 mg daily	100 mg orally o.d.	100 mg o.d.	100 mg o.d. before meals	25-100 mg o.d.	100 mg o.d. in morning[6]	100 mg o.d.[10]	100 mg/day	-
	Saxagliptin	2.5-5 mg daily	2.5-5 mg daily	5 mg o.d.	-	25-100 mg daily	-	5 mg/day[10]	-	-
	Alogliptin	-	-	-	-	-	-	12.5-25 mg[10]	12.5-25 mg/day	-
GLP receptor agonist	Exenatide	0.01-0.02 mg s/c inj, before meals	5-10 µg s/c b.i.d. inj, within 60 min before a meal	s/c inj	5-10 µg b.i.d., 30-60 min before meals	5-10 µg b.i.d. s/c up to 60 min before main meals	5-10 µg b.i.d. within 60 min of morning and evening meals[7]	-	5-10 µg b.i.d., s/c, 60 min prior to meals	-
	Exenatide QW	-	-	-	-	-	Once weekly[7]	Once weekly[10]	Once weekly	-
	Liraglutide	s/c inj o.d.	Started at 0.6 mg injectable dose	s/c inj once-daily	-	-	-	Once-daily[10]	0.6-1.8 mg/day	-
	Albiglutide	-	-	-	-	-	30 mg weekly[7]	-	-	-
	Dulaglutide	-	-	-	-	-	-	Once weekly[10]	-	-
	Semaglutide	-	-	-	-	-	-	-	Once weekly	-
	Lixisenatide	-	-	-	-	-	-	-	-	-

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SGLT2 inhibitor	Dapaglifozin	-	-	o.d.	-	-	-	-	-	-
	Canagliflozin	-	-	-	-	-	-	-	-	-
	Ipragliflozin	-	-	-	-	-	-	-	-	-
Dopamine D2 receptor agonist	Bromocriptine	1.6-4.8 mg, with food in the morning within 2 h of awakening	-	0.8-4.8 mg o.d., early in the morning	-	-	-	1.6-4.8 mg o.d. within 2 h after waking in the morning, with food[9]	-	Within 2 h of rising in the morning
Amylin analog	Pramlintide	15-60 µg s/c inj in type 1 DM, 60-120 µg s/c inj in type 2 DM. Injected prior to meals	15-60 µg s/c inj in type 1 DM, 60-120 µg s/c inj in type 2 DM. Injected immediately before eating	s/c inj before meal	15-60 µg s/c inj before meals as an adjunct to insulin in DM type 1 cases and 60-120 µg s/c inj before meals with insulin in type 2 DM.	60-120 µg t.i.d. (for DM type 2), 15-30 µg (for DM type 1), s/c before meals	60-90 µg, 3-4 times/day s/c prior to meals (type 1 DM). Higher doses s/c b.i.d. in type 2 DM[7]	-	-	15-60 µg before meals in type 1 DM; max 120 µg before meals in type 2 DM
Bile acid binding resin	Colesevelam	3 tab (625 mg) b.i.d. before lunch and dinner or 6 tab prior to largest meal	1,875 mg b.i.d. or 3,750 mg o.d. orally	-	-	-	-	-	-	-

2 describing only frequency of administration. Timing of administration was reported by 5 books. Metformin SR preparation was listed by only 3 textbooks, both American in origin, though its use is widespread across the world. Pioglitazone usage is covered in 7 textbooks, with similar dosages, but relationship with meal timings is not stated by any author.[6]

Rosiglitazone, which is used in a restricted subset of patients, is covered by 5 texts. But none of the textbooks mention timings of this drug. The omission of this molecule's details from majority of endocrinology and diabetology books reflects the decline in its popularity. Meglitinide analogs are discussed in uniform detail by all 9 textbooks surveyed. This is a pleasant (and perhaps superfluous) exercise, as nateglinide is rarely used in clinical practice and repaglinide is relatively less commonly prescribed than sulfonylureas.

Sulfonylureas are the oldest class of glucose-lowering drugs currently in use. A large number of drugs and preparations are available, and are well-covered by most textbooks. Micronized glyburide, glipizide ER and gliclazide, which are not available in all countries, are discussed by relatively less authors (5 and 4, respectively). While information related to glipizide and glibenclamide is uniform in most books, there is conflicting advice regarding the frequency of dosage of glimepiride. Timing of administration is not mentioned by many authors. A blanket recommendation to prescribe all sulfonylureas 20-30 minutes before meals is given by the leading Indian textbook of diabetes. The maximum dose of glimepiride is mentioned as 6 mg by three, and 8 mg by six authors. This may reflect the difference in maximum doses approved by various regulatory authorities. A similar lack of consensus is seen for gliclazide, where maximum doses vary from 240 to 320 mg and frequency of dosage ranges from 1 to 3 per day.

Alpha-glucosidase inhibitors are discussed in detail by seven (acarbose), four (miglitol) and two (voglibose) authors. Most of the advice contained in these texts is concordant with each other. The dipeptidyl peptidase-4 (DPP-4) inhibitors are relatively newer class of drugs, which may explain why their dose is not mentioned in many texts. The timing of administration; however, is written differently in various books. While some authors omit this aspect of posology, others recommend vildagliptin and sitagliptin before meals, and yet others advise no regard to meal times. The glucagon-like peptide-1 (GLP-1) receptor agonists are covered by some, but not all, books. While exenatide's timing of administration is discussed by six authors, no book makes mention of the timing of dosage of liraglutide. New once-weekly GLP-1 receptor agonists are discussed by one (dulaglutide, semaglutide) and three (exenatide QW) textbooks. Bromocriptine and colesevelam are nondiabetic drugs, which have recently been approved for use in type 2 diabetes. They are prescribed infrequently. While four books mention bromocriptine, in a uniform manner, only two US textbook covers colesevelam. This poor coverage reflects the poor availability of this molecule. Another molecule which has limited availability, relevance and usage, is pramlintide. Approved for the management of postprandial hyperglycemia in both type 1 and type 2 diabetes, this is well-described, in a similar manner, by five texts. Sodium glucose co-transporter 2 (SGLT2) inhibitors, which are the latest class of oral glucose-lowering drugs, have found mention in one current US pharmacology textbook.

CONCLUSION

This bibliometric analysis highlights the need to have standardized, uniform sources of information regarding posology of glucose-lowering drugs. Such information will be of importance to students and professionals of diabetology, and will benefit their patients as well.

LIMITATIONS

All textbooks of pharmacology, diabetology and endocrinology were not analyzed for the review. However, the textbooks analyzed here are the most commonly used ones.

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CLINICAL STUDY

Study of Thyroid Function Tests in Patients with Metabolic Syndrome

BALVIR SINGH*, PAWAN KUMAR VISHWAKARMA†, ABHINAV GUPTA†, RAM PRATAP SINGH†, CHANDRA PRAKASH†

ABSTRACT

Background: The metabolic syndrome is a constellation of clinical and metabolic abnormalities including abdominal obesity, hypertension, dyslipidemia and impaired fasting glucose or impaired glucose tolerance. Metabolic syndrome and thyroid dysfunction are independent risk factors for cardiovascular disease. **Aims and objectives:** To study the prevalence, symptomatology of thyroid dysfunction and fine needle aspiration cytology (FNAC) findings of thyroid in the patients having metabolic syndrome. **Material and methods:** The study was carried out in 60 cases of metabolic syndrome (according to NCEP ATP III criteria) selected from the medicine outdoor clinic (including diabetic clinics, thyroid clinics) and medicine indoor wards in Post Graduate Department of Medicine, SN Medical College and Hospital, Agra. Diagnosis of thyroid dysfunction was made by history, examination and serum FT4 and TSH. **Result and observations:** Out of 60 patients of metabolic syndrome, 30 patients (50%) were euthyroid, 13 patients (21.66%) had subclinical hypothyroid and 12 patients (20%) had overt hypothyroid. Five patients (8.33%) of metabolic syndrome had hyperthyroidism. Truncal obesity was most prevalent (80.0%) component of metabolic syndrome, followed by hypertriglyceridemia (70%). Diabetes mellitus was equally prevalent in both males as well as females and was present in about 40.0% patients and 53% of patients with metabolic syndrome were hypertensive. **Conclusion:** This study shows that 50% metabolic syndrome patients had thyroid dysfunction. About 21.66% had subclinical hypothyroidism, 20% had overt hypothyroidism and 8.33% were having hyperthyroidism. The most common symptom in metabolic syndrome patients with hypothyroidism was lethargy/sleepiness followed by dry and coarse skin. The most common symptom in hyperthyroid patients was nervousness (100%) followed by sweating, heat intolerance and palpitation in 80% of the

Keywords: Metabolic syndrome, subclinical hypothyroid, hypothyroid, hyperthyroid

The metabolic syndrome is a constellation of clinical and metabolic abnormalities including abdominal obesity, hypertension, dyslipidemia and impaired fasting glucose or impaired glucose tolerance. All these manifestations are surrogate markers of insulin resistance which is the crux abnormality associated with metabolic syndrome. Thyroid hormones markedly stimulate the basic metabolic rate and the metabolism of carbohydrate, lipids and proteins. This hormone appears to serve as a general pacemaker accelerating metabolic process and may be associated with metabolic syndrome. It also plays an important role in the development of the reproductive system. As metabolic syndrome and thyroid dysfunction (subclinical or overt hypothyroidism and hyperthyroidism) are independent risk factors for cardiovascular disease, it is possible that patients suffering from both these disease entities may have a compounded risk.

AIMS AND OBJECTIVES

The aim of this study was to determine the prevalence, symptomatology of thyroid dysfunction and fine needle aspiration cytology (FNAC) findings of thyroid in the patients having metabolic syndrome.

MATERIAL AND METHODS

In our study, 60 patients of metabolic syndrome without liver disease (viral, alcoholic, drug, autoimmune, etc.), chronic renal disease, pancreatitis and pregnancy were studied. Their clinical (age, sex, family history and blood pressure), biochemical (thyroid-stimulating hormone [TSH], free thyroxine [FT4], lipid profile, blood sugar) and thyroid FNAC profiles were studied. According to the National Cholesterol Education

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Program Adult Treatment Panel III (NCEP ATP III) at least three of the following criteria should be present to diagnose metabolic syndrome:

- Elevated waist circumference: Men - ≥90 cm for Indians, Women - ≥80 cm for Indians.
- Elevated triglycerides: ≥150 mg/dL.
- Reduced HDL ("good") cholesterol: Men - <40 mg/dL, Women - <50 mg/dL.
- Elevated blood pressure: ≥130/85 mmHg.
- Elevated fasting glucose: ≥110 mg/dL.

The thyroid hormone assays (FT4 and TSH) were done using enzyme-linked immunosorbent assay (ELISA), and fasting blood sugar, triglycerides and high-density lipoprotein cholesterol (HDL-C) were done enzymatically on Roche Automated Clinical Chemistry Analyzer.

Diagnosis of thyroid dysfunction was made by FT4 and TSH - *Euthyroid:* normal TSH and normal FT4; *Subclinical hypothyroidism:* high TSH and normal FT4; *Hypothyroidism:* high TSH and low FT4 and *Hyperthyroidism:* low TSH and high FT4.

OBSERVATIONS AND RESULTS

Our study group consisted of 24 male (40%) and 36 (60%) female patients. Male-to-female ratio was 2:3. Majority of patients (40.0%) belonged to age group 40-49 years. Mean age of all the patients was 47.6 ± 7.5 years. The mean age of males and females was 49.6 ± 8.0 and 46.2 ± 7.1, respectively.

The prevalence of components of metabolic syndrome (Fig. 1) in men and women were, central obesity in 18 (75%) and 30 (83.3%) patients, respectively; low HDL-C in 12 (50%) and 28 (77.8%) patients, respectively; high triglycerides in 18 (75%) and 24 (66.7%), respectively; impaired fasting glucose (>100 mg/dL) or diabetes in 12 (50.0%) and 12 (33.3%), respectively and elevated blood pressure in 18 (75%) men and 32 (88.9%) women.

Out of 60 patients of metabolic syndrome (Fig. 2), 30 patients (50%) were euthyroid, 13 patients (21.66%) had subclinical hypothyroid and 12 patients (20%) had overt hypothyroid while 5 patients (8.33%) had hyperthyroid.

The most common symptom (Table 1) in both subclinical and overt hypothyroid patients was (77.77%) lethargy (sleepiness) followed by dry and coarse skin (72.22%), cold intolerance (66.66%), puffiness of face (66.66%), constipation (61.11%), depression (55.55%) and body aches (55.55%). Weight gain was seen in 50% and

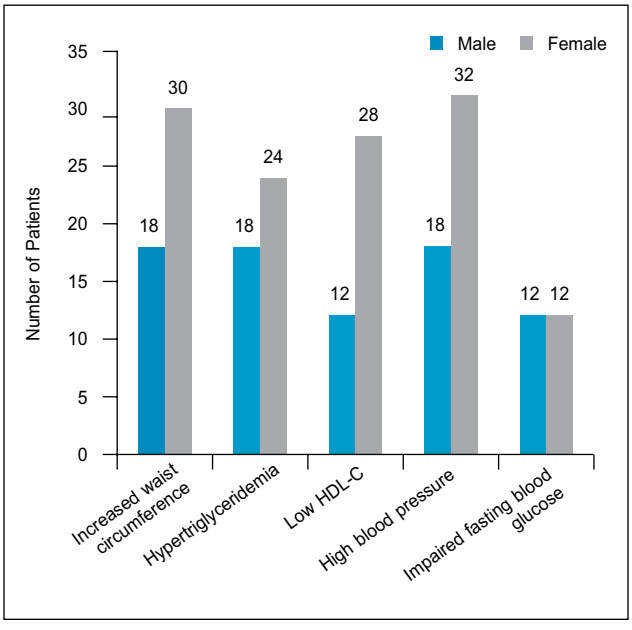

Figure 1. Different components of metabolic syndrome in the study group.

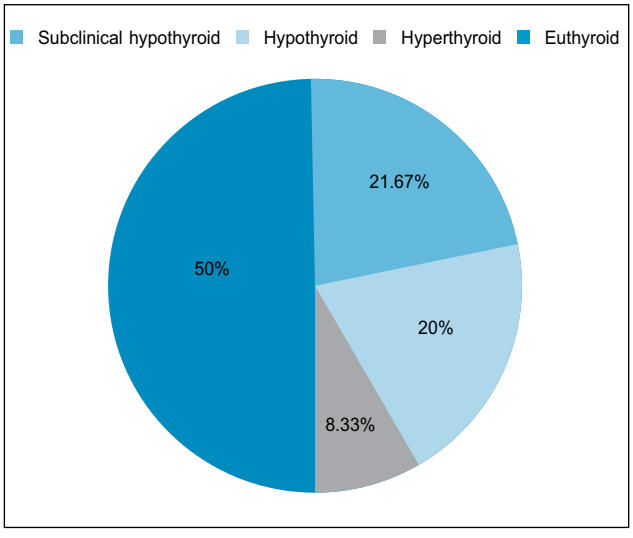

Figure 2. Thyroid dysfunction in study group.

paresthesia in 44.44% hypothyroid patients. Thyroid gland size was enlarged in (33.33%) 6 patients. Five hypothyroid females (35.71%) had menorrhagia. Hair loss was present in 5 patients (27.77%).

The total number of hyperthyroid patients was 5 in the study. The commonest symptom (Table 2) was nervousness (100%) in our patients. Other symptoms like sweating (80%), hypersensitivity to heat (80%) and palpitation (80%) were also common in these patients. Fatigue, weight loss and enlarged thyroid (goiter) were present in 3 patients (60%). One male and 1 female hyperthyroid patient had hyperdefecation.

Table 1. Prevalence of Symptomatology of Hypothyroidism in the Study Group

Symptoms	Male (n = 4)		Female (n = 14)		Total (n = 18)	
	No.	%	No.	%	No.	%
Lethargy/ Sleepiness	3	75	11	78.57	14	77.77
Dry and coarse skin	3	75	10	71.42	13	72.22
Cold intolerance	2	50	10	71.42	12	66.66
Puffiness of face	2	50	10	71.42	12	66.66
Body aches	2	50	8	57.14	10	55.55
Weight gain	2	50	7	50	9	50
Constipation	2	50	9	64.28	11	61.11
Depression	2	50	8	57.14	10	55.55
Paresthesia	2	50	6	42.85	8	44.44
Menorrhagia	-	-	5	35.71	5	27.77
Thyroid gland size enlarged	1	25	5	35.71	6	33.33
Hair loss	1	25	4	28.57	5	27.77

Table 2. Prevalence of Symptomatology of Hyperthyroidism in the Study Group

Symptoms and signs	Male (n = 2)		Female (n = 3)		Total (n = 5)	
	No.	%	No.	%	No.	%
Nervousness	2	100	3	100	5	100
Sweating	2	100	2	66.66	4	80
Hypersensitivity to heat	1	50	3	100	4	80
Palpitation/ Increased heart rate	2	100	2	66.66	4	80
Fatigue	1	50	2	66.66	3	60
Goiter	1	50	2	66.66	3	60
Hyperdefecation	1	50	1	33.33	2	40
Weight loss	1	50	2	66.66	3	60

Twelve thyroid dysfunction patients with metabolic syndrome underwent FNAC of thyroid gland. Out of 12 patients, 8 patients (66.66%) had normal cytological findings. Two (1 subclinical hypothyroid and 1 overt hypothyroid) patients had simple colloid goiter and 1 overt hypothyroid had nodular colloid goiter. One hyperthyroid patient with metabolic syndrome had nodular hyperplasia of thyroid gland.

DISCUSSION

In our study, out of 60 patients of metabolic syndrome, 30 patients (50%) were euthyroid, 13 patients (21.66%) had subclinical hypothyroid and 12 patients (30%) had overt hypothyroid. Five patients (8.33%) of metabolic syndrome had hyperthyroidism. A cross-sectional study from South India by Shantha et al has shown prevalence of subclinical hypothyroidism as 21.9% and overt hypothyroidism in 7.4% cases of metabolic syndrome.

The female-to-male ratio in our study was 2.25:1 in subclinical hypothyroidism and 2:1 in overt hypothyroidism patients. The female-to-male ratio in hypothyroidism ranges from 2:1 to 8:1 in various epidemiological surveys. Some surveys indicate hypothyroidism to be more prevalent in elderly population, reaching as high as 20%. Shrestha et al observed the association of metabolic syndrome in 21, 5 and 6 cases in 48 euthyroid, 24 hyperthyroid and 28 hyporthyroid groups, respectively.

The commonest symptom in hypothyroid patients was lethargy (77.77%). This was consistent with case-control study by Khurram et al in which 67.9% cases had lethargy. In our study too, dry and coarse skin was mentioned by 72.22% of patients like 70-79% cases in another study. Similarly, cold intolerance, that was found in 89% of patients in one series and 93% of another series, was prevalent in 66.66% of our cases, which is quite comparable to the 58.25% in Watanakunakorn's. Five out of 14 (35.71%) females had menorrhagia as in the study by Khurram et al. In a cohort study by Scott and Mussey, 28 women (56%) complained of menstrual disturbance, with the most common complaint being menorrhagia (occurring in 18 [36%] of the women). Other symptoms like body aches, weight gain, constipation, paresthesia, hair loss were similar to what has been described in various studies.

In our study, 66.66% patients had puffiness of face as compared to 63.3% in the study by Khurram et al, 79% in Lerman's series and 67% in Watanakunakorn's series.

Thyroid was enlarged in 6 hypothyroid patients (33.33%) as compared to 6.6% in the study by Samanta.

The most common symptom in hyperthyroid patients was nervousness (100%), followed by sweating (80%),

hypersensitivity to heat (80%), palpitation (80%), weight loss (60%), fatigue (60%), hyperdefecation (40%) and goiter (60%), which was statistically comparable with the study by Trivalle et al.

Out of 12 patients who underwent FNAC of thyroid, 8 patients (66.66%) had normal cytological findings. Two (1 subclinical and 1 overt) hypothyroid patients had simple colloid goiter and 1 overt hypothyroid patients had nodular colloid goiter. One hyperthyroid patient with metabolic syndrome had nodular hyperplasia of thyroid gland.

In this study, we found that out of 60 patients of metabolic syndrome, 24 (40%) were male and 36 (60%) were female. Male-to-female ratio was 2:3 proving that disease was more dominant in females. Most of the patients of metabolic syndrome were belonging to age group 40-60 years. Mean age of males was 49.6 ± 8.0 years and mean age of female patients was 46.2 ± 7.1 years. Mean age of patients with metabolic syndrome in a study by Bacon and colleagues was 47 years and similarly another study also noted mean age of 54 years. About 23.3% of the patients met all the five diagnostic components of metabolic syndrome. Waist circumference was elevated in almost all (80%) the cases. Other components of metabolic syndrome were distributed in 50-70% of the patients.

Majority of male patients (45%) had waist circumference in range of 90-100 cm. Mean waist circumference of males was 97.9 ± 7.2 cm. Most of the female patients (40%) also had waist circumference in 90-100 cm range. Mean waist circumference of female patients was 97.8 ± 2.1 cm. In previous studies, mean waist circumference of males and females was 102 cm and 92 cm, respectively. About 62% of the patients had triglyceride level between 150 and 174 mg%. Only 14.3% had elevated triglyceride level more than 200 mg%. Mean triglyceride level of males was 160.1 ± 22.6 mg%. Mean level of triglyceride in females was 162.7 ± 27.2 mg%. Liese et al noted hypertriglyceridemia in 50% of the cases. In previous studies, it was observed that mean triglyceride level in the patients of metabolic syndrome was 191.8 mg%.

About half of the patients (50.0%) had HDL level between 30 and 39 mg/dL. Mean HDL level of males was 40.8 ± 6.4 mg/dL. Female patients had mean HDL level 43.4 ± 7.5 mg/dL. There was a significant variation in mean HDL level between male and female patients. Similar studies in the past observed HDL abnormalities in 63.5% of the patients. In our study, 40% patients of metabolic syndrome were diabetic. Only 8.3% patients had blood sugar in impaired glucose tolerance (IGT) range, 16.6% patients were newly diagnosed diabetics. Maximum number of patients (41.7%) were diabetic for duration more than 10 years. Matteoni et al also performed a similar study and found diabetes mellitus in 23% of cases.

In our study, 53% of patients with metabolic syndrome were hypertensive. In all, 25% were newly diagnosed hypertensives. About 37.5% had hypertension for duration more the 10 years. Kaplan and colleagues noted prevalence of hypertension in 58% patients of metabolic syndrome.

CONCLUSION

The present study concludes that 50% metabolic syndrome patients had thyroid dysfunction. Subclinical hypothyroidism was present in 21.66% and overt hypothyroidism 20% patients. Hyperthyroidism was observed in 8.33% of metabolic syndrome patients.

The most common symptom in metabolic syndrome patients with hypothyroidism was lethargy/sleepiness followed by dry and coarse skin.

The most common symptom in hyperthyroid metabolic syndrome patients was nervousness (100%) followed by sweating, heat intolerance and palpitation (80%). Thyroid dysfunction patients with metabolic syndrome presenting with goiter underwent FNAC of thyroid - 8 patients (66.66%) had normal cytological findings. Two (1 subclinical and 1 overt) hypothyroid patients had simple colloid goiter and 1 overt hypothyroid patient had nodular colloid goiter. One hyperthyroid patient with metabolic syndrome had nodular hyperplasia of thyroid gland.

Metabolic syndrome and thyroid dysfunction are independent risk factors for cardiovascular disease. Their co-existence may even compound the risk of cardiovascular events. Hence, it is worthwhile to screen metabolic syndrome patients for thyroid dysfunction at the earliest for further decrease in cardiovascular events.

SUGGESTED READING

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OBSERVATIONAL STUDY

Negative Pressure Wound Therapy in Infected Wounds – Indian Public Hospital Observational Study

RAM MURMURE*, MILIND RUKE†

ABSTRACT

Introduction: Negative pressure wound therapy (NPWT) is a procedure in which vacuum is used to enhance wound healing. Vacuum-assisted closure (VAC) refers to wound dressing that uses pressure below normal continuously or intermittently to the surface of a wound. The negative pressure is maintained by an apparatus; this promotes healing in various kinds of wounds and also helps in wound debridement. **Aims:** This study was carried out with an aim to find out the rate of wound contraction, compare infection clearance, granulation tissue formation and to study postoperative pain after using NPWT. **Material and methods:** All types of infected wounds with slough were selected. Patients irrespective of sex between 18 and 70 years of age were included. The wounds included were traumatic, diabetic foot, varicose ulcer, infected wounds, carbuncle, etc. The procedure included surgical debridement as a preliminary procedure, followed by application of NPWT. The wound criteria: 1) size, 2) shape, 3) wound margin and floor, 4) edge and contraction were studied. **Results and Discussion:** Infected wounds can be treated by specific modalities like daily wound dressing, surgical debridement, hyperbaric oxygen therapy and NPWT. NPWT seems more efficient than standard wound care for infected wounds. In our study, the mean size of ulcer in diabetic patients before NPWT was found to be 6.33 × 4.52 cm; after application of NPWT, it was 4.7 × 2.95 cm. The mean size of ulcer in traumatic patients before NPWT was found to be 7.1 × 5.1 cm, while after application of NPWT, it was 5 × 3.63 cm. The mean size of ulcer in vascular patients was found to be 5.71 × 3.85 cm before NPWT, and after application of NPWT, it was 4 × 2.42 cm. NPWT dressings have been proven to be beneficial as a variant method of dressing, mainly by negative pressure which sucks out serous fluid and helps in the formation of granulation tissue. Used in various wounds, continuous suction over period of time and later intermittent suction depending on wound status enhance wound healing process and lead to faster recovery compared to conventional methods of dressing. **Conclusion:** The wound healing period for large traumatic wounds and chronic diabetic wounds is 123 days as per published data. In our study, where NPWT was used, the average wound healing period was 35 days, ranging between 10 and 62, which is statistically significant ($p < 0.005$). NPWT is cost-effective, reduces hospital stay of patient with minimal chances of limb amputation with better results than standard wound care.

Keywords: Vacuum-assisted closure, hyperbaric oxygen therapy, negative pressure wound therapy

Negative pressure wound therapy (NPWT) is a relatively novel method used for managing wounds, both acute and chronic.[1] Vacuum-assisted closure (VAC), or NPWT, uses vacuum to improve wound healing. VAC involves wound dressing that applies pressure below normal, continuously or intermittently, to the surface of a wound.[2-4] The negative pressure promotes healing in different types of wounds.[5-7] It also assists with wound debridement. Wound healing is best at negative pressure of 85-125 mmHg. Application of negative pressure removes fluid, decreases edema and enhances blood flow, and decreases bacterial counts. It is less costly than traditional management of infected wounds.[8-13]

A negative pressure of 50-125 mmHg lowers the interstitial pressure, and fluid and debris from the wound gets sucked into a collection chamber.[14-18] In the beginning, the vacuum is continuous, but as the drainage is reduced, the vacuum is applied intermittently. The vacuum dressing is usually changed at approximately 2- to 6-dayinterval.[19-25]

AIMS AND OBJECTIVES

This study was carried out with an aim to find out rate of wound contraction, compare infection clearance, granulation tissue formation and to study postoperative pain after using NPWT. The study also aimed to

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determine the length of hospital stay and to evaluate the cost-effectiveness of the procedure and effect on amputation prevention.

MATERIAL AND METHODS

Source of Data

- Patients of Grant Government Medical College and JJ Hospital, Mumbai, Maharashtra.
- A total of 50 cases clinically presenting as ulcer between June 2017 and December 2019 were included in the study.

Inclusion Criteria

- Both male and female
- Patients between 18 years and 70 years.
- Patients who signed informed written valid consent to be included in the study.
- Patients having acute or chronic wounds, including traumatic wounds, varicose ulcer, bed sore, diabetic wounds.

Exclusion Criteria

- Age less than 18 or above 70 years.
- Patients on chemotherapy or suffering from malignancy.
- Suspected poor compliance.
- If the patient did not sign the consent form.
- Peripheral vascular disease wound with acute or chronic osteomyelitis.

Procedure

Preparation of the wound

After cleaning the wound, foam dressing was cut to shape and kept into the wound cavity. The wound was then sealed with an adhesive dressing ensuring that the drapes covered the foam and tubing and 3 cm of healthy skin.

Negative pressure application

Negative pressure was applied to the wound using vacuum pump (Fig. 1), which delivered continuous or intermittent pressures, ranging from 50 to 125 mmHg. The foam dressing squeezed to the negative pressure. The pressure was applied continuously for the first 48 hours and then changed.

RESULTS AND DISCUSSION

The study was done on 50 patients in Dept. of Surgery, JJ Hospital Mumbai, Maharashtra.

In our study, as shown in Table 1, the mean size of ulcer in diabetic patients before VAC was found to be 6.33 × 4.52 cm, while after the application of VAC, it appeared to be 4.75 × 2.9 cm; the mean size of ulcer in traumatic patients before VAC was found to be 7.1 × 5.1 cm, and after application of VAC, it appeared to be 5 × 3.63 cm; the mean size of ulcer in vascular patients was found to be 5.71 × 3.85 cm before VAC, and after application of VAC, it appeared to be 4 × 2.42 cm. The p value was <0.05 and it was statistically significant. Figure 2 shows diabetic foot infection and Figure 3 depicts necrotizing fasciitis before and after treatment.

VAC therapy is an alternative to routine wound management.

In our study, average age of wounds was 35 days. In a study by Caniano et al,[26] average age of wounds was 37 days and in that by Ulusal et al,[27] it was 32 days, as compared to 59 days with standard dressing. In our study, the mean duration of wound healing was found to be 35.2 days with standard deviation (SD) of 12.03 days. In a study by Zimny et al,[28] the mean duration of wound healing was found to be 123.4 days with

Figure 1. VAC instrument.

Table 1. Mean Ulcer Size (cm) Before and After VAC Therapy in Wounds of Different Etiology

Etiology	Before VAC		After VAC	
	Length (cm)	Breadth (cm)	Length (cm)	Breadth (cm)
Diabetic	6.33	4.52	4.75	2.95
Traumatic	7.1	5.1	5	3.63
Vascular	5.71	3.85	4	2.42

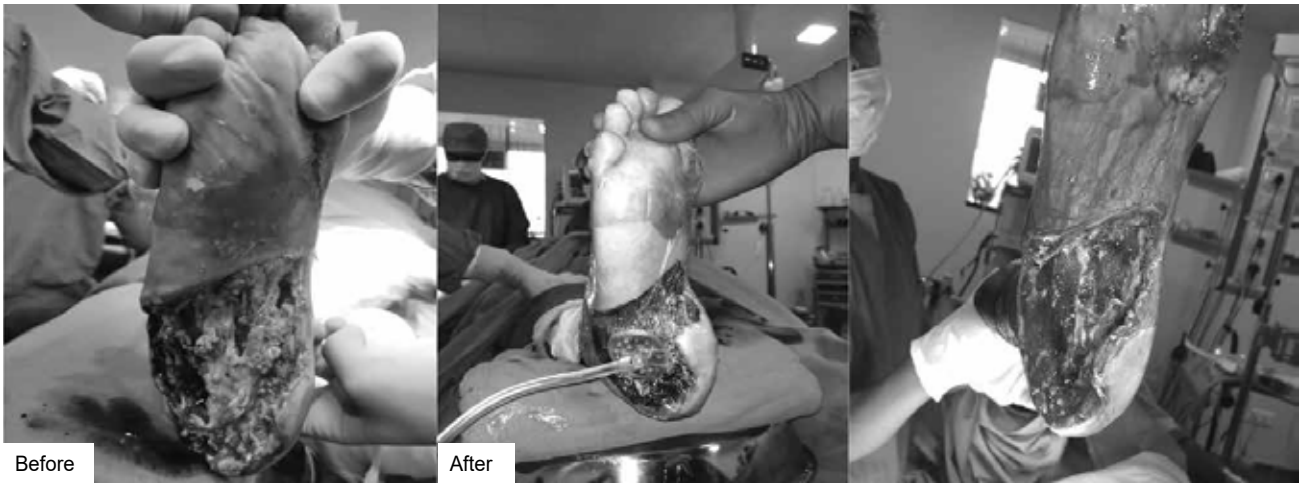

Figure 2. Diabetic foot infection (biofilm).

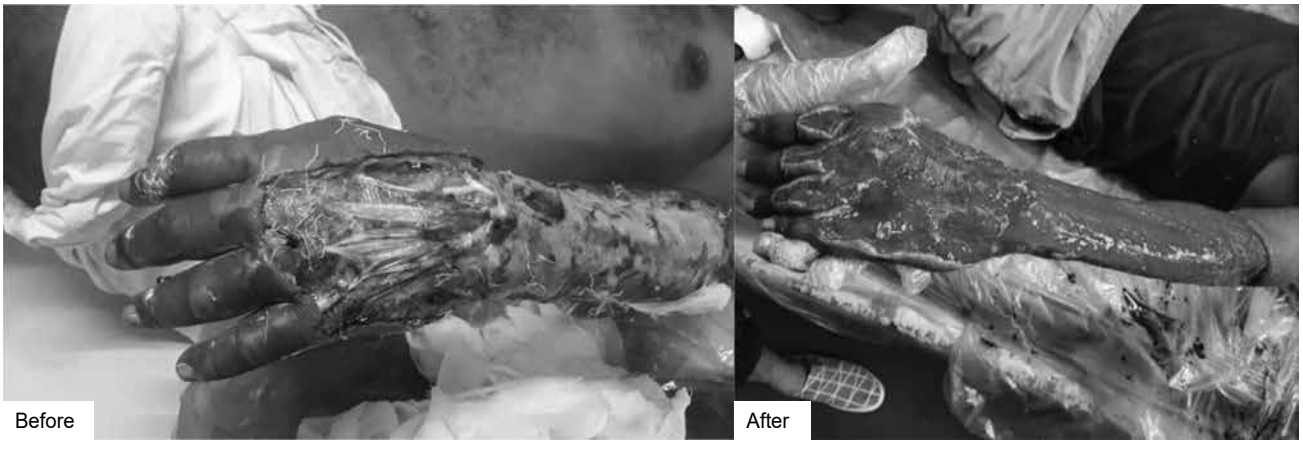

Figure 3. Necrotizing fasciitis.

SD of 10.5 days. On statistical analysis, the p value was calculated to be <0.00001, which is statistically significant with 95% confidence interval (CI).

The wound healing period for large traumatic wounds and chronic diabetic wounds is 123 days as per published data.[28] In our study, where NPWT was used, the average wound healing period was 35 days.

Many mechanisms are suggested. VAC works by increasing the local blood flow and diminishes the edema fluid and colonization rates. The procedure promotes wound closure as it accelerates the formation of granulation tissue and also via mechanical effects on the wound.[29] It provides a clean moist wound and removes excess wound fluid, thus giving way to an ideal wound healing environment. In our study, out of 50 patients, 36 patients had wound over foot region, 12 patients had wound over back region.

NPWT provides a moist wound environment, favoring granulation of edge of ulcer. A moist wound bed promotes re-epithelialization, action of growth factors, angiogenesis. A moist wound environment also limits local pain, protecting the nerve endings and enhancing quality of life. Decrease in edema limits interstitial pressure and has a positive impact on microvascular occlusion and lymphatic drainage, thus enhancing the availability of nutrients, oxygen and antibiotics in the wound area.[30]

CONCLUSION

From our study, it can be concluded that NPWT is useful in wound healing in various types of wounds; therefore, NPWT should be the modality of choice in management of infected wounds. Vacuum-assisted dressing is more effective than traditional wound dressing. NPWT, in combination with surgical debridement and antibiotic therapy, is effective in managing infected wounds.

The wound healing period for large traumatic wounds and chronic diabetic wounds is 123 days as per published data. In our study, where NPWT was

used, the average wound healing period was 35 days, ranging between 10 and 62 days, which was statistically significant ($p < 0.005$).

NPWT is cost-effective, reduces hospital stay of patient with minimal chances of limb amputation with better results than standard wound care.

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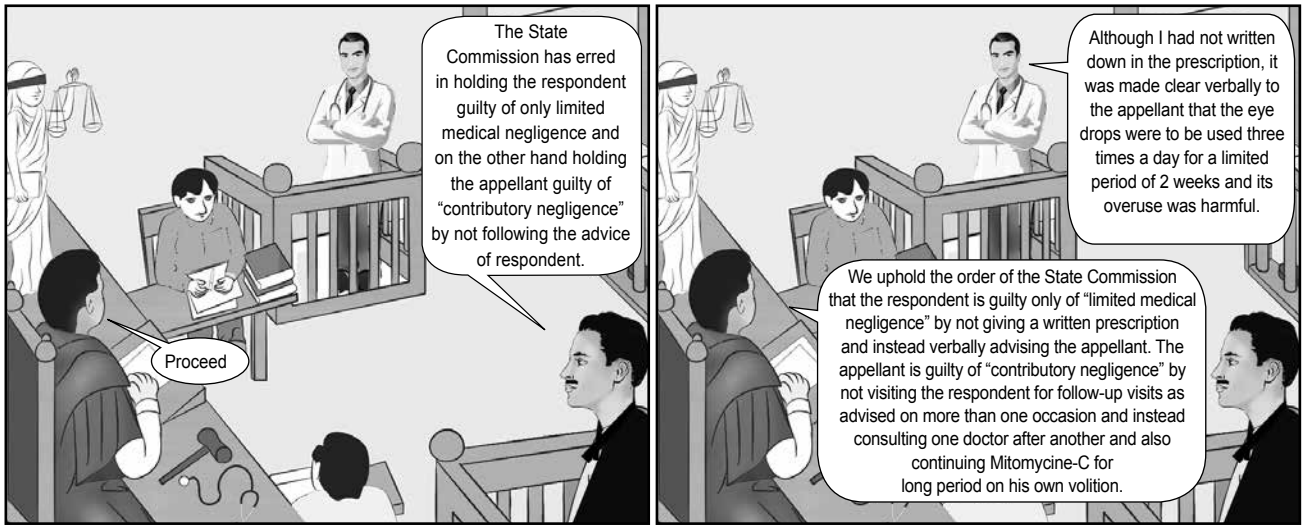
Case of Limited Negligence on Part of the Doctor and Contributory Negligence by the Patient



Lesson: The order dated 31.08.2006 in Complaint Case No. C-21/95 of the State Consumer Disputes Redressal Commission Delhi stated "By not prescribing in writing in the prescription that medicine Mitomycine-C should be used, at first instance, only for 2 weeks, OP has committed an offence of limited medical negligence as complainant also cannot be excused for contributory negligence by not approaching the treating doctor after few days and hopping from one doctor to another and continued using the medicine for long resulting in dry-eye syndrome causing loss of vision in the eye."

COURSE OF EVENTS

- June 1993: Following a minor complaint of a cosmetic nature in his left eye, the appellant consulted respondent, who is an eye surgeon, in his clinic in Daryaganj, who after examining him informed that he was suffering from an innocuous growth known as pterygium and since there was likelihood that the growth may increase, excision was advised through a minor surgery, which would ensure that the appellant's eye would become normal within 5 days. Appellant, therefore, agreed to undergo this surgery.
- October 1993: The respondent conducted the surgery on the appellant at his clinic and the appellant was thereafter prescribed medicines for both local application, which included Mitomycine-C, as also oral medication. However, soon after, the appellant's left eye became red and there was acute pain and irritation, which persisted, and therefore he consulted the respondent, who assured him that if he continues to regularly use Mitomycine-C, his eye would become normal. However, during the course of using this medicine, appellant's eye further deteriorated and became very dry and there was loss of vision in that eye. Appellant complained about this to the respondent, who changed the medicine, which only further aggravated the condition.
- The appellant consulted another ophthalmologist Dr G, who informed him that his left eye had become very dry due to wrong prescription of Mitomycine-C and he was advised to consult Dr P at Hospital A, New Delhi.
- Dr P confirmed that the eye had got damaged due to prolonged use of Mitomycine-C.
- The appellant thereafter went to hospital B where this diagnosis was confirmed by a cornea

specialist, Dr A. He was advised to stop using all the medicines, including Mitomycine-C.

- Being aggrieved because of the medical negligence and deficiency in service on the part of respondent, because of which the appellant's eye became dry, he issued a legal notice to respondent to pay him Rs. 10 Lakhs as compensation but received no response.
- Appellant, therefore, approached the State Commission with a complaint of medical negligence and deficiency in service against respondent and requested that he be directed to pay Rs. 10 lakhs as damages and compensation since there was total loss of vision in appellant's left eye, which had adversely affected both his professional and personal life, as also any other relief as deemed appropriate.
- Respondent on being served filed a written rejoinder denying the above allegations, which he termed as false, frivolous and vexatious. It was contended that appellant approached him with a condition known as pterygium, which is a growth of extra skin and if it reached the pupil area of the eye, it could permanently hamper the appellant's vision. Surgery was, therefore, necessary, which was satisfactorily conducted. The appellant thereafter advised both oral medication as also medicine through local application.
- After a week, when the healing of the appellant's eye was completed, respondent advised the respondent to use Mitomycine-C for 2 weeks since this was necessary to prevent recurrence of pterygium. This medicine, which comes in the form of injection, was converted into eye drops for use three times a day and appellant was verbally told that over use of this medicine for more than 2 weeks is harmful.
- Unfortunately, the appellant did not heed this advice and instead of coming back for a further check up appears to have continued using Mitomycine-C and taking treatment from various other doctors as per his own whim and fancy.
- It was only on 03.03.1994 i.e. after over 4 months that appellant visited the respondent and told him that he was still continuing the use of Mitomycine-C. Respondent immediately asked him to discontinue the same and to come back after 15 days.
- The appellant again did not heed this advice and consulted the respondent after 3 months i.e. on 22.06.1994 when he was prescribed natural tear drops and lacri-lube ointment.
- A perusal of these facts clearly indicate that it was the appellant who was responsible for the damage caused to his left eye by prolonged use of Mitomycine-C on his own volition and against medical advice given by respondent. There was, therefore, no deficiency in service or medical negligence of respondent.
- The State Commission after hearing the parties and on the basis of evidence produced before it held the respondent guilty of "limited negligence" by not advising the appellant in writing to use Mitomycine-C only for a particular limited period. The relevant part of the order of State Commission reads as follows:

"By not prescribing in writing in the prescription that medicine Mitomycine-C should be used, at first instance, only for 2 weeks to OP has committed an offence of limited medical negligence as complainant also cannot be excused for contributory negligence by not approaching the treating doctor after few days and hopping from one doctor to another and continued using the medicine for long resulting in dry-eye syndrome causing loss of vision in the eye. OP is guilty of this limited medical negligence amounting to deficiency in service due to which the complainant has lost his vision of one eye though he can also be not absolved from contributory negligence which is a mitigating circumstance for awarding compensation."

The State Commission, therefore, held that a lump-sum compensation of Rs. 50,000/- to the appellant would meet the ends of justice.

- Being aggrieved by the lesser compensation, the present first appeal has been filed before National Consumer Disputes Redressal Commission (NCDRC).

ALLEGATION OF THE APPELLANT

- Learned counsel for the appellant contended that the State Commission erred in holding the respondent guilty of only limited medical negligence and on the other hand holding the appellant guilty of "contributory negligence" by not following the advice of respondent.
- Following the surgery, the appellant did visit the respondent doctor for further check-up prior to 03.03.1994. According to appellant, respondent had prescribed him Mitomycine-C on 18.10.1993 and the prescription did not indicate either the duration for taking the medicine or its possible harmful side effects.

- The appellant was also not advised when he should come back for a follow-up check. Further, when the appellant visited the respondent on 03.03.1994 with a serious complaint regarding his operated eye, respondent again sought to hide the correct facts by recording that the condition of appellant's eye as also the vision was normal.
- Since the appellant had already started losing his eyesight and he was having acute pain in his eye, he was constrained to approach other doctors, who advised the appellant to immediately stop the use of Mitomycine-C. It was these doctors who informed him that the problem in his left eye had occurred due to over use of Mitomycine-C, which should not have been used for more than 2 weeks.
- Counsel for the appellant further stated that the conduct of the respondent was suspect before the State Commission as is evident from the fact that he did not produce the necessary documents on the ground that these had been destroyed in a fire. Because of the medical negligence and callousness on the part of respondent, appellant lost the vision in his left eye causing him a great deal of mental agony and adversely affecting his work as a senior clerk in the Supreme Court of India.

REJOINDER OF THE RESPONDENT

- Learned counsel for respondent denied the above allegations and stated that it is not factually correct that respondent had prescribed Mitomycine-C to the appellant on 18.10.1993 i.e. immediately following the surgery. In fact, he was prescribed other medicines and ointments after the surgery and it was only after a week when the eye had healed that Mitomycine-C was prescribed to the appellant.
- It is a proven fact in ophthalmology medical literature that Mitomycine-C is successful in checking the recurrence of pterygium, which has a very high incidence of recurrence and is routinely prescribed for limited periods following such surgeries. It was under these circumstances that respondent rightly prescribed this medicine to the appellant. Although not written down in the prescription, it was made clear verbally to the appellant that the eye drops were to be used three times a day for a limited period of 2 weeks and its over use was harmful.
- This is further confirmed by the fact that respondent converted only one vial of Mitomycine-C injection into eye drops, which would have lasted at the most for a little over 2 weeks. From this fact alone, it is clear that the Appellant had been procuring this medicine and getting it converted into eye drops from some other doctor(s) and in this way using it for several weeks i.e. till 03.03.1994 when he next visited the respondent, who immediately directed him to discontinue the use of this medicine.
- Learned counsel for respondent pointed out that a senior ophthalmologist of hospital A, Dr M, has confirmed to him in writing that appellant had consulted him and also informed him that he was continuing to use Mitomycine "on his own".
- Appellant continued to disregard medical advice of Respondent even after 03.03.1994 by not coming for follow-up visits, which he was advised to do by respondent, who had prescribed him some other medicines and wanted to assess their effect.
- From the above facts, it is clear that appellant, who was not an illiterate person and who had been clearly orally advised to use Mitomycine-C eye drops only for a limited duration by respondent, failed to follow this advice and continued to use the medicine on his own, for which respondent cannot be held responsible, particularly since appellant did not even come for the follow-up visit after 2 weeks. There was no medical negligence or deficiency in service on the part of respondent, who had prescribed the right medicine and given correct advice regarding its limited period of use. The present first appeal, therefore, having no merit deserves to be dismissed.

OBSERVATIONS OF NCDRC

- The appellant visited the respondent's clinic with a complaint in his left eye and was detected with pterygium, for which a minor surgery was conducted is not in dispute.
- It is also a fact that appellant was prescribed Mitomycine-C by respondent, which is a drug of choice, to ensure that pterygium does not recur since it has a high degree of recurrence.
- While it is a fact (as also observed by the State Commission) that no directions were given by respondent in writing to appellant regarding the duration for which the drug should be used or any written precaution against its prolonged use, we find force in the contention of respondent that since he had converted only one vial of Mitomycine

injection into eye drops, this itself indicates that the intention was clearly for its limited use for about 2 weeks and not for several months.

- When specifically asked by us, learned counsel for the appellant also fairly conceded that respondent had converted only one vial of Mitomycine injection into eye drops, thus confirming the respondent's clear intention regarding its use for a limited period. It is, thus, apparent that appellant had been using this medicine for several weeks by getting the Mitomycine injection converted into eye drops through some other source and not by the respondent, for which respondent cannot be held responsible.
- It was under these circumstances that the State Commission had held the respondent guilty of only "limited medical negligence" for not having put down in writing the dosage and duration of the medicine in the prescription slip.

ORDER OF THE NCDRC

We agree with this finding. We further agree that the appellant is guilty of "contributory negligence" by not visiting the respondent for follow-up visits as advised on more than one occasion and instead consulting one doctor after another and also continuing Mitomycine-C for long period on his own volition, which resulted in the dry eye syndrome and consequent loss of vision in the left eye. To sum up, we uphold the order of the State Commission that respondent is guilty only of "limited medical negligence" by not giving a written prescription and instead verbally advising the appellant, for which a compensation of Rs. 50,000/- is reasonable and we, therefore, confirm the same. The present first appeal is dismissed. Respondent is directed to pay a sum of Rs. 50,000/- to the appellant within 6 weeks, failing which it will carry interest @ 6% per annum for the period of default. No costs.

REFERENCE

1. Case no. 692 of 2006, NCDRC; Order date 16.01.2013.

■■■■

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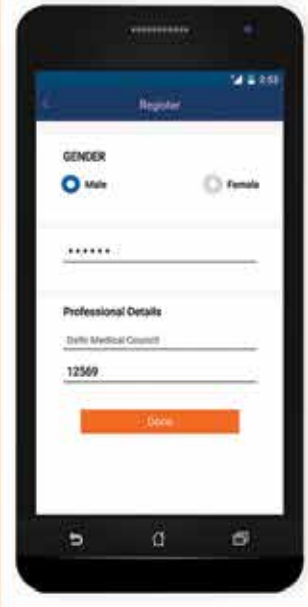

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