METABOLIC CLINICS OF NORTH INDIA

Fortis C-DOC Centre of Excellence for Diabetes, Metabolic Diseases & Endocrinology

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Editor-in-Chief Message

"This is fourth issue of a newsletter named 'Metabolic Clinics of North India'. Our goal is to create a forum for exchange of latest information on diabetes and metabolic diseases. It is our mission to use our academic resources for prevention and management of diabetes, obesity, metabolic syndrome and endocrine disorders and their complications in Asian Indians. The purpose of this newsletter is to keep you updated with latest advancements in the field."

Dr Anoop Misra
Chairman; Fortis CDOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology

Effectiveness of intermittent fasting in the treatment for overweight and obesity in adults

A systematic review was conducted by Harris and his colleagues to examine the effectiveness of intermittent energy restriction in treatment of overweight and obesity in adults, when compared to usual care treatment or no treatment. This review published in the journal *JBI Database System Rev Implement Rep.* in 2018 included overweight or obese (BMI ≥25 kg/m) adults (≥18 years). Intermittent energy restriction was defined as consumption of ≤800 kcal on at least one day, but no more than six days per week. Intermittent energy restriction interventions when compared with no treatment or usual care (continuous energy restriction ~25% of recommended energy intake). Studies included were randomized and pseudo-randomized controlled trials. The primary outcome of this review was change in body weight. Secondary outcomes included: i) anthropometric outcomes (change in BMI, waist circumference, fat mass, fat free mass); ii) cardiometabolic outcomes (change in blood glucose and insulin, lipoprotein profiles and blood pressure); and iii) lifestyle outcomes: diet, physical activity, quality of life and adverse events.

A systematic search was conducted with help of electronic databases for published studies, protocols and trials. Evaluation of quality of included studies was done using the standardized critical appraisal instruments from the Joanna Briggs Institute. Data extraction was using the standardized data extraction tool from the Joanna Briggs Institute.

Six studies were included in this review. The intermittent energy restriction regimens varied across studies and included alternate day fasting, fasting for two days, and up to four days per week. The duration of studies ranged from three to 12 months. Four studies included continuous energy restriction as a comparator intervention and two studies included a no treatment control intervention.

Systemic review showed that intermittent energy restriction was more effective than no treatment for weight loss. Intermittent energy restriction was shown to be more effective than no treatment, however, this should be interpreted cautiously due to the small number of studies and future research is warranted to confirm the findings of this review.

Harris *et al.*; Intermittent fasting interventions for treatment of overweight and obesity in adults: a systematic review and meta-analysis; *JBI Database System Rev Implement Rep.* 2018 Feb; 16(2):507-547. https://www.ncbi.nlm.nih.gov/pubmed/29419624

Expert Comments

It appears that intermittent fasting has resulted in weight loss compared to usual diet. This systemic review clearly states that it is not superior to usual calorie restricted diets. Interestingly religious intermittent fasting may not be the same since uncontrolled intake of energy from different sources than grain is allowed there.

Dr. Anoop Misra; Chairman; Fortis C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology

Effect of whey protein intake on postprandial glycemia

The study done by King *et al.* published in *American Journal of Clinical Nutrition* investigated postprandial glycemic and appetite responses after small doses of intact and hydrolyzed whey protein co-ingested with mixed-nutrient breakfast and lunch meals in men with type 2 diabetes. In a randomized, single-blind crossover design, 11 men with type 2 diabetes mean age: 54.9 ± 2.3 years; glycated hemoglobin: 6.8% ± 0.3% attended the laboratory on 3 mornings and consumed 1) intact whey protein (15 g), 2) hydrolyzed whey protein (15 g), or 3) placebo (control). Protein was consumed immediately before mixed-macronutrient breakfast and lunch meals, separated by 3 hours. Blood samples were collected periodically and were processed for insulin, intact glucagon-like peptide 1 (GLP-1), gastric inhibitory polypeptide (GIP), leptin, peptide tyrosine tyrosine (PYY3-36), and amino acid concentrations. Interstitial glucose was measured during and for 24 h after each trial. Subjective appetite was assessed with the use of visual analog scales.

Total postprandial glycemia area under the curve was reduced by 13% after breakfast following the intact whey protein whereas hydrolyzed whey attenuated early glucose after breakfast when compared with control. Post lunch glycemia improved after the intact whey protein only when compared with control. Greater satiety was observed after the intact whey protein only after both meals when compared with control. Insulin concentrations increased after both the intact and hydrolyzed whey protein, showing strong positive correlations with increases in valine and isoleucine.

The consumption of a small 15-g dose of intact whey protein immediately before consecutive mixed-macronutrient meals improves postprandial glycemia, stimulates insulin release, and increases satiety in men with type 2 diabetes.

King *et al.*; A small dose of whey protein co-ingested with mixed-macronutrient breakfast and lunch meals improves postprandial glycemia and suppresses appetite in men with type 2 diabetes: a randomized controlled trial; *Am J Clin Nutr.* 2018 Apr 1; 107(4):550-557. https://www.ncbi.nlm.nih.gov/pubmed/29635505

Expert Comments

There is a considerable amount of data on the health benefits of whey protein supplementation. This study has shown that intake of small amounts (15 g) of whey protein intake immediately before a major meal increases insulin secretion, promotes satiety and attenuates postprandial glycemic excursion in people with well controlled diabetes of short duration.

Dr. Ritesh Gupta; Additional Director; Fortis C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology

Canagliflozin and renal outcomes in type 2 diabetes and nephropathy

Perkovic *et al.* conducted a double-blind randomized trial published in *The New England Journal of Medicine* on patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes.

4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group. The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P < 0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P = 0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P = 0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P < 0.001). There were no significant differences in rates of amputation or fracture.

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years.

Perkovic *et al.*; Canagliflozin and renal outcomes in type 2 diabetes and nephropathy; *NEJM*;2019. https://www.nejm.org/doi/full/10.1056/NEJMoa1811744

Expert Comments

The recently presented and published CREDENCE Trial has created a furore and drawn wide applause from the section of the medical fraternity that is involved in the care of patients with diabetes and chronic kidney disease. The results clearly demonstrate that canagliflozin, a member of the SGLT2 inhibitor class of drugs, cuts the risk of renal failure and death in patients who have diabetic kidney disease to the tune of 30%. Moreover, it attenuates the rate of decline of estimated glomerular filtration rate (eGFR) by an impressive figure of 2.7 ml per minute in comparison to patients not taking canagliflozin. The drug holds the potential to be an important addition to the therapeutic arsenal of diabetologists and nephrologists, particularly for patients who have Stage 3 or Stage 4 diabetic nephropathy. Interestingly, it took 17 long years after the angiotensin receptor blockers (ARBs), for a new therapy to appear on the horizon, that can slow down the progression of chronic kidney disease in patients with diabetes.

Dr. Atul Luthra; Additional Director; Fortis C-DOC; Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology; FMRI, Gurgaon

FDA issues warning against homeopathic products

Products labeled as homeopathic have not been approved by the Food and Drug Administration (FDA) for any use and may not meet modern standards for safety, effectiveness and quality. Products labeled as homeopathic can be made from a wide range of substances, including ingredients derived from plants, healthy or diseased animal or human sources, minerals and chemicals. These products are often marketed as natural, safe and effective alternatives to approved prescription and nonprescription products and are widely available in the marketplace. These unapproved drugs may cause significant and even irreparable harm if they are poorly manufactured, which can lead to contamination, or may contain active ingredients that are not adequately tested or disclosed to patients, such as belladonna, which the agency has previously warned against. The US FDA released warning letters sent to five homeopathic product manufacturers because of significant good manufacturing practice (GMP) violations. These companies jointly manufacture and package Puriton Eye Relief Drops, which are labeled as homeopathic. The FDA tested multiple samples and found these eye drops were non-sterile, which could lead to an eye infection, and had a high pH level, which could lead to eye injury such as glaucoma, corneal scarring and loss of vision.

"These unapproved drugs may cause significant and even irreparable harm if they are poorly manufactured, which can lead to contamination, or may contain active ingredients that are not adequately tested or disclosed to patients," FDA said.

Expert Comments

FDA Center for Drug Evaluation and Research (CDER) is the watchdog for potential medications seeking approval for its usage. In order for CDER to begin evaluating a drug, pharmaceutical companies first should do extensive testing that includes:

1. Preclinical studies in animals- to generate pharmacodynamic, pharmacokinetic and toxicological effect of drug.
2. Clinical trials- testing the drug on humans. And then document the results for the drug.

Herbal supplements and homeopathic drugs are regulated by the FDA, but not as drugs, they fall under a category called dietary supplements.

Dr. Vimal Gupta; Consultant; Fortis C-DOC
Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology

Can Americans trust generic drugs?

America needs generic drugs. They make up 90% of the American drug supply. Reports say that there are serious compromises behind the production of generic drugs, and the FDA's limits as a global regulatory agency. Mr. Baker an auditor inspecting the Indian manufacturing plants that make many of America's low-cost generic drugs. He visited a plant in Aurangabad run by the Indian company Wockhardt, which made about 110 generic-drug products for the American market.

He caught an employee trying to smuggle out a garbage bag of documents. The documents led Mr. Baker to discover that the plant had knowingly released into Indian and other foreign markets vials of insulin containing metallic fragments. These had apparently come from a defective sterilizing machine. He learned that the company had been using the same defective equipment to make a sterile injectable cardiac drug for the American market. Two months after Mr. Baker's Wockhardt inspection, the FDA banned the import of drugs from that plant into the United States, a potential $100 million loss in sales for the company.

Over the next five years, first in India and then in China, uncovered fraud or deceptive practices were discovered in almost four-fifths of the drug plants inspected. Some of the plants used hidden laboratories, secretly repeated tests and altered results to produce fake data that fundamentally misrepresented drug quality, then submitted that data to regulators. In some instances, deceptions and other practices contributed to generic drugs with toxic impurities, unapproved ingredients and dangerous particulates reaching American patients. There were majority of the unannounced inspections; the investigators found things the plants no longer had time to fix: Infestations of birds and insects. A pile of critical manufacturing records, tossed in a trash bin. An employee bathroom near a sterile manufacturing area in one plant lacked drainage piping, so urine puddled directly onto the floor.

Expert Comments

Generic drugs are cheaper, but are they of high quality? This question comes to my mind when I prescribe medicines to patients. Unfortunately according to this report substantial proportion of generic drugs are not quality controlled in India.

Dr. Anoop Misra; Chairman; Fortis C-DOC;
Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology

Novel insights: sourdough bread

Sourdough bread is the oldest and most original form of leavened bread made by the fermentation of dough using naturally occurring lactobacilli and yeast.

Sourdough bread (100 g):

Energy-277.9 kcal;	Carbohydrate-50 g;
Starch-45.4 g;	Total sugar-4.5 g;
Soluble fiber- 0.3 g;	Insoluble fiber-4.9 g;
Dietary fiber-5.2 g;	Protein-9 g;
Fat-4.3 g	

Sourdough bread has a low glycemic index value of 53.

Sourdough fermentation has deep effects on rheology, sensory and shelf life attributes of baked goods as reported by Gobbetti *et al*. Some aspects such as the potential to lower glycemic index, increased mineral bioavailability and decreased the gluten content have been proven almost definitively, others potentialities are emerging. Reviews reports the main evidence on the use of sourdough fermentation for salt reduction in baked goods, management of irritable bowel syndrome (IBS), synthesis/release of bioactive compounds, especially the metabolism of phenolic compounds, and exploitation of the potential of non-conventional flours (legumes and pseudo-cereals) and milling by-products (bran and germ).

Gobbetti *et al.*; Novel insights on the functional/nutritional features of the sourdough fermentation; *Int J Food Microbiol*; May 2018. https://doi.org/10.1016/j.ijfoodmicro.2018.05.018

Expert Comments

Research shows that sourdough bread has improved flavor, low glycemic index and gluten free making it a good option for diabetic and celiac patients as well. It keeps blood sugar and insulin levels low. Moreover, the low phytate content makes nutrient absorption better such as calcium, magnesium, iron and zinc.

Bhavya Arora; Clinical Nutritionist & Certified Diabetes Educator
Fortis C-DOC; Centre of Excellence for Diabetes,
Metabolic Diseases and Endocrinology

Commentary on 'Violence on Doctors' by Dr. Anoop Misra published in Hindustan Times can be accessed on the following link

https://healthshots.hindustantimes.com/expert-speak/first-do-no-harm-to-doctors

Recent Alerts on Drug/Lifestyle/Nutrition

- **The US Food and Drug Administration (FDA) has added a boxed warning to the label for gout drug febuxostat. The FDA has concluded that there is an increased risk for death with febuxostat compared to another gout medicine, allopurinol.**
  (https://www.fda.gov/Drugs/DrugSafety/ucm631182.htm)
- **Canagliflozin reduces risk of renal failure and death 30% in patients with type 2 diabetes.**
  (Perkovic *et al.*; Canagliflozin and renal outcomes in type 2 diabetes and nephropathy; *NEJM*;2019.)
- **Large quantities of grapefruit juice (*Chakotra* in Hindi) can prolong QT interval ,which increases chances of heart irregularity**
  (https://www.medscape.com/viewarticle/913187)

Metabolic Clinics of North India

This newsletter by the name of **Metabolic Clinics of North India** aims to give relevant and interesting information for physicians. Articles, abstracts, quiz/puzzles, interesting novel recipes, wisdom pearls and informative pictures are most welcome. The content shall be edited and reviewed by the editorial board and the Chief Editor.

Few areas of discussions have been mentioned below; any other innovative suggestions apart from these will be welcome.

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Areas of Discussion : Epidemiology, Diagnosis, Drug Treatment, Insulin/Monitoring of blood sugar, Complications of diabetes, Diet/Exercise, Important trials, Interesting case reports, New discoveries, Research highlights from India

Send in your queries/feedback at: Email Id: mcnifortis2017@gmail.com (Address to Bhavya Munjal) Do mention your full name, designation, phone number and location

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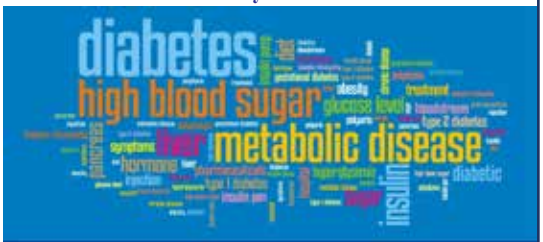

Diabetes with Delight

A Joyful Guide to Managing Diabetes in India

Anoop Misra
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First with Galvus Met

Basic Succinct Statement
GALVUS®MET

Presentation: Tablets containing vildagliptin/metformin hydrochloride fixed dose combination: 50 mg/500 mg, 50 mg/850 mg, 50 mg/1,000 mg. **Indications:** ♦ Galvus®Met is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM) whose diabetes is not adequately controlled on metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. ♦ Galvus®Met is indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea. ♦ Galvus®Met is indicated in combination with insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycemic control. ♦ Galvus®Met is also indicated for the treatment of Type 2 Diabetes mellitus having HbA1c > 8% where diabetes is not adequately controlled by diet and exercise alone. **Dosage and administration:** ♦ Do not exceed the maximum recommended daily dose of vildagliptin (100 mg). ♦ Should be given with meals. ♦ **Adults:** Starting dose for patients inadequately controlled on vildagliptin or metformin hydrochloride monotherapy: 50 mg/500mg twice daily and gradually titrated after assessing the adequacy of therapeutic response. ♦ Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets: 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg based on the dose of vildagliptin or metformin already being taken. ♦ Starting dose for treatment naive patients: may be initiated at 50 mg/500 mg daily and gradually titrated to a maximum dose of 50 mg/1,000 mg bid after assessing the adequacy of therapeutic response. ♦ Use in combination with a sulfonylurea or with insulin: the dose of Galvus®Met should provide vildagliptin dosed as 50 mg twice daily (100 mg total daily dose) and a dose of metformin similar to the dose already being taken. ♦ **Renal impairment:** Dosage adjustment may be required in patients with creatinine clearance between 30 and 90 ml/min. ♦ **Geriatric patients:** Dosage should be adjusted based on renal function ♦ **Children (under 18 years of age):** Not recommended. **Contraindications:** Known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients ♦ patients with creatinine clearance <30 ml/min ♦ **congestive heart failure** ♦ acute or chronic metabolic acidosis including lactic acidosis or diabetic ketoacidosis with or without coma ♦ should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. **Warnings and precautions:** ♦ Risk of lactic acidosis. ♦ Monitoring of renal function before treatment initiation and regularly thereafter. ♦ Caution with concomitant use of medications that may affect renal function or metformin hydrochloride disposition. ♦ Galvus®Met should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials. ♦ Discontinue treatment in case of hypoxemia. ♦ Temporary discontinuation in patients undergoing surgical procedure. ♦ Excessive alcohol intake to be avoided. ♦ Not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5x the upper limit of normal. Liver function tests (LFT) to be performed prior to treatment initiation, at three-month intervals during the first year and periodically thereafter. Withdrawal of therapy with Galvus®Met recommended if an increase in AST or ALT of 3x upper limit normal or greater persist. Following withdrawal of treatment with Galvus®Met and LFT normalisation, treatment with Galvus®Met should not be reinitiated. ♦ Risk of decreased vitamin B12 serum levels. ♦ Should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. ♦ Risk of hypoglycemia. ♦ May be temporarily withheld in case of loss of glycemic control. ♦ Elderly patients' renal function should be assessed more frequently. ♦ Not recommended in pediatric patients. **Women of child-bearing potential, pregnancy:** Should not be used in pregnancy unless the potential benefit justifies the potential risk to the fetus. **Breast-feeding:** Should not be used during breast-feeding. **Adverse reactions:** ♦ **Vildagliptin:** Rare cases of angioedema. Rare cases of hepatic dysfunction (including hepatitis). ♦ **Vildagliptin monotherapy** – Common: dizziness – Uncommon: headache, constipation, oedema peripheral. ♦ **Metformin monotherapy** – Very common: loss of appetite, flatulence, nausea, vomiting, diarrhoea, abdominal pain. Common: dysgeusia. Very rare: lactic acidosis, hepatitis, skin reactions such as erythema, pruritus and urticarial, decrease of vitamin B12 absorption, liver function test abnormalities. ♦ Other effects with **combination of vildagliptin and metformin** - Common: tremor, dizziness, headache. ♦ Other effects with **combination of Vildagliptin and Metformin with insulin** – Common: headache, nausea, gastroesophageal reflux disease, chills, blood glucose decreased – Uncommon: diarrhoea, flatulence. ♦ Other effects with **combination of vildagliptin and metformin with a sulfonylurea** – Common: dizziness, tremor, asthenia, hypoglycemia, hyperhidrosis. ♦ **Post-marketing experience:** – Rare: hepatitis (reversible upon drug discontinuation) – Unknown: urticaria, bullous and exfoliative skin lesions including bullous pemphigoid, pancreatitis, arthralgia, sometimes severe. **Interactions:** ♦ Interactions with vildagliptin: low potential for drug interactions, no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin. ♦ Interactions with metformin hydrochloride: furosemide, nifedipine, cationic drugs, drugs tending to produce hyperglycemia, alcohol. ♦ **Packs:** Box containing 6 strips of 10 tablets each. ♦ **Note:** Before prescribing, consult full prescribing information available from Novartis Healthcare Private Limited, Sandoz House, Dr. Annie Besant Road, Worli, Mumbai- 400 018, Tel: 022 2495 8888. For the use only of a registered medical practitioner or a hospital or a laboratory. India BSS dtd 12 Jan 17 based on international BSS dtd 28 Nov 16, effective from 29 May 17.

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Novartis/CVM/Galvus_Ad/1053073/26/10/2018

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