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# Medical Bulletin

## News You Can Use

## Cartilage Degeneration Algorithm Predicts Progression of Osteoarthritis

Osteoarthritis (OA) is a joint disease that deteriorates the articular cartilage (the soft cushion between the bony surfaces of a joint). OA constitutes a significant financial burden: it cannot be cured by current treatments, and the disease often leads to joint replacement surgery, which is highly expensive.

**Current imaging methods, such as MRIs or X-RAYs, only provide information on the thickness or composition of the cartilage, but they fail to provide data on the risk of OA or tools to predict its progression.**

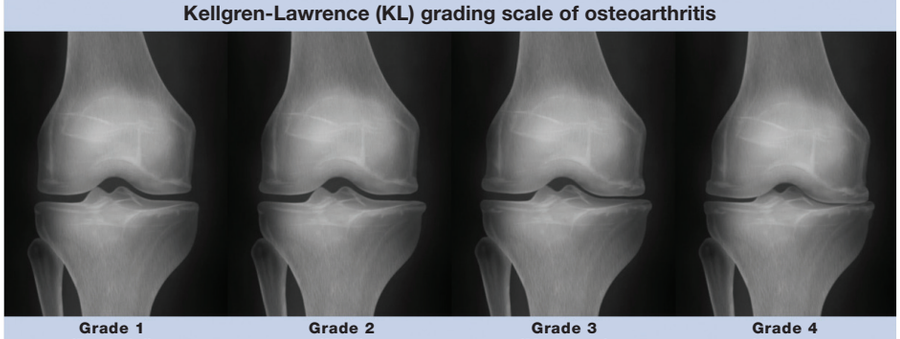
**A novel cartilage degeneration algorithm can predict the progression of OA in individual patients,** according to new research from the University of Eastern Finland. **This new algorithm could greatly facilitate clinical decision-making in the treatment of OA.**

**The degeneration algorithm is based on stresses experienced by the knee joint during walking, and these were simulated on a computer. The algorithm assumes that stresses exceeding a certain threshold during walking will cause local degeneration in the articular cartilage of the knee.**

**The researchers tested the ability of their cartilage degeneration algorithm to predict the subject-specific development and progression of OA and separate groups with different OA levels** (patients without OA, patients with mild OA, and patients with severe OA). At the start of the follow-up, all patients were OA-free. The algorithm was applied at the onset of the follow-up, and the findings were compared against the four-year follow-up data. **Based on the prognosis from the simulation and the experimentally defined Kellgren-Lawrence grades four years later, the researchers found that the algorithm was able to categorise patients into their correct groups.** Maximum degeneration and degenerated volumes within cartilage were significantly higher ($P < 0.05$) in OA compared to healthy subjects.

**This degeneration algorithm shows great potential in predicting patient-specific progression of OA in the knee, and could facilitate clinical decision-making in the treatment of osteoarthritis.** The algorithm could be used to clinically simulate the effects of various interventions, including osteotomy, meniscectomy, and weight loss, on the progression of osteoarthritis.

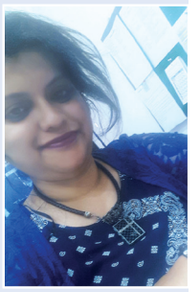
**Kellgren-Lawrence (KL) grading scale of osteoarthritis**



Grade 1 (Doubtful) | Grade 2 (Mild) | Grade 3 (Moderate) | Grade 4 (Severe)

| CLASSIFICATION | Normal | Doubtful | Mild | Moderate | Severe |
|---|---|---|---|---|---|
| DESCRIPTION | No features of OA | Minute osteophytes; doubtful significance | Definite osteophytes; normal joint space | Moderate joint space reduction | Joint space greatly reduced; subchondral sclerosis |

## Greetings from Blue Cross Laboratories!



*Dear Colleagues,*

*Hope all of you are in the best of health and spirit, and my heartiest wishes to you and your families for a fabulous 2018 !*

*It gives me immense pleasure and satisfaction to present you with the last issue of the Blue Cross Medical Bulletin for this current financial year.*

*This issue will have you updated on a few recent medical discoveries/developments, and clinical insights involving novel discoveries/avenues in diverse therapeutic facets. We have also included two brief tutorials and a new segment called* "Beyond the Pharmacodynamic Frontier"*, in which we will highlight therapeutic benefits of molecules extending beyond the realm of their current indications and efficacy. We hope all these topics make for interesting reading !*

*I am sure you would enjoy reading this edition of the Medical Bulletin as you did in the past. Please do remember to send in your feedback, so that we can incorporate the same in future editions.*

*Happy Reading!*

*Wishing you and your families a wonderful 2018 !*

*Cheers!*

*Best wishes & Warm regards,*

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Short Tutorial

# GERD: An Upcoming Lifestyle Disorder

- In this day and age, various medical conditions (e.g., obesity, glucose intolerance, hypercholesterolemia, coronary heart disease) stem from one or more disturbed ways of daily living.
  - o A sedentary lifestyle coupled with very little exercise, alcohol and nicotine, disturbed and/or inadequate sleep along with ubiquitous psychogenic factors play a pivotal role in disturbing the homeostasis of activities of daily living.
- **Gastroesophageal Reflux Disease (GERD)** is also gradually evolving into a lifestyle disorder.
  - o **GERD is a common medical condition characterized by the development of chest and epigastric symptoms because of reflux of gastric components into the esophagus.**
    - The most common esophageal symptoms are heart burn, acid regurgitation, dysphagia, and chest pain.
    - Extra-esophageal symptoms include cough, voice change, nausea and asthma.
  - o **As one of the most common gastro-intestinal diseases,** it affects 13-19% of the people worldwide and has a greater prevalence in the western world, with population-based studies suggesting a prevalence of 10-40% in North America and Western Europe. Interestingly, **the trend in the affluent sections of society in a country like India matches closely to that of affluent countries themselves !**
  - o Symptoms of GERD can cause lifestyle disturbances by affecting patients daily functioning and sleep, **which may lead to a significant decrease in patient's quality of life.** Persistent GERD is known to lead to complications such as Barrett's esophagus, esophageal strictures and adenocarcinoma.
  - o **The cost associated with the management of this disease also represents a significant burden on health systems.** It has been estimated that the annual cost of health care and lost productivity because of GERD in the United States alone approximates 24 billion (outpatient's visits, hospitalizations, emergency department utilization and pharmacy costs).
  - o **Diagnosis:** There currently exists no definitive, simple diagnostic test for GERD. **The presence of clinical symptoms alone is an indication for treatment with a 2 week trial of proton pump inhibitor (PPI) therapy.** Patients without improvement of symptoms may be considered for an ambulatory pH monitoring and/or endoscopy to establish a more definitive diagnosis.
    - **The most common finding on esophago-gastro-duodenoscopy (EGD) is non-erosive reflux disease** in which there is no endoscopic evidence of macroscopic esophagitis.
    - **Non erosive disease has been associated with higher occurrence of functional gastrointestinal disorders and esophageal acid hypersensitivity.**
    - Erosive reflux disease which is characterized by the presence of mucosal breaks in the lower esophagus on performing endoscopy is less commonly observed. In cases when endoscopy is normal, pH measurement with or without impedance studies may demonstrate esophageal acid reflux.
  - o **NON-PHARMACOLOGICAL MANAGEMENT**
    - **The first-line therapy for patients with GERD is dietary modifications:**
      - **A diet with a positive association with GERD:** A high intake of vegetables, legumes, fruits, whole grains, fish and olive oil, moderate amounts of dairy products, and low amounts of red or processed meat.
      - **Weight loss.**
      - **Avoid alcohol and tobacco.**

**Gastrointestinal Dysmotility Occasionally Coexists with GERD**

- **Approximately 40%-50% of patients with GERD have abnormal peristalsis.** This dysmotility is particularly severe in about 20% of patients because of very low amplitude of peristalsis and/or abnormal propagation of the peristaltic waves (ineffective esophageal motility).
  - o Esophageal clearance is slower than normal, therefore, the refluxate is in contact with the esophageal mucosa for a longer period of time and it is able to reach more often the upper esophagus and pharynx.
  - o These patients are prone to mucosal injury (including Barrett's esophagus) and frequent extra-esophageal symptoms such as cough.

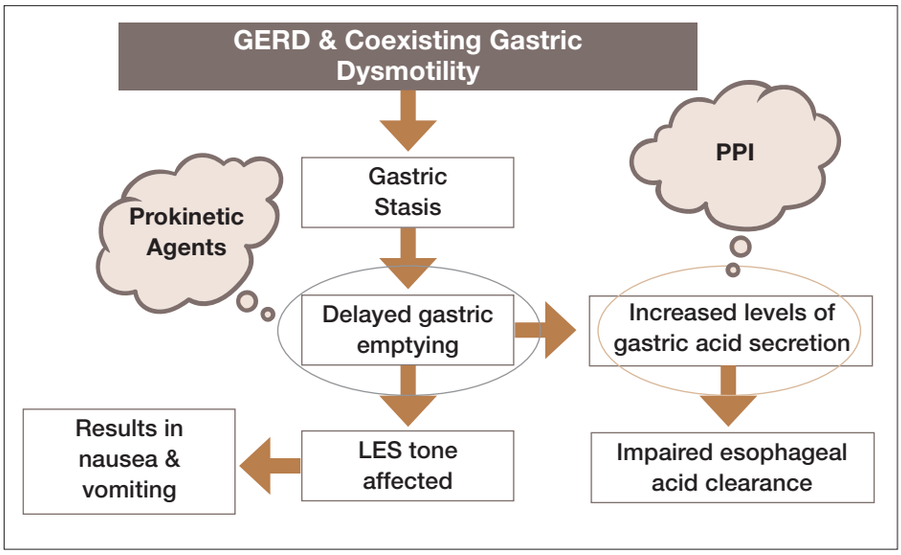
**Principles of GERD Pharmacotherapy**

- **GERD is primarily a disorder of esophageal motility, as most patients with GERD do not secrete abnormal quantities of gastric acid.**
- **The treatment of GERD, however, is typically not directed at the underlying pathophysiology but rather at reducing the acid content of the refluxate.**
- If a less acidic fluid contacts the esophageal mucosa, the balance between offensive and defensive forces is shifted toward the side of mucosal protection.
- **An effective therapy for GERD should accomplish the following goals.**
  1. **Control of symptoms.**
  2. **Heal esophageal mucosal damage** (erosive esophagitis), which does not necessarily correlate with presence or severity of symptoms.
  3. **Prevent complications of chronic reflux,** including esophageal stricture, ulceration, and blood loss.
  4. **Improve esophageal and gastric**

**motility** with prokinetic agents. Prokinetic agents are medications that enhance coordinated gastrointestinal motility and transit of content in the gastrointestinal tract, mainly by amplifying and coordinating the gastrointestinal muscular contractions.

- **Currently the predominant pharmacological therapy for GERD is acid suppression, making PPIs among the most widely prescribed medications for decades.** PPIs are proven to be safe, effective, and well tolerated.
- **The prokinetic agent domperidone is a dopamine receptor (D2) antagonist which increases tone of the LES, stops reflux of acidic content into the esophagus and improves upper GI peristalsis.** Unlike metoclopramide, domperidone does not cross the blood–brain barrier and thus has a better safety profile, with no significant CNS side effects.

**The combination of PPI and prokinetic agent is a rational choice for GERD coexisting with GI dysmotility.**




Short Tutorial

## C-Peptide Test: What is It? Why is It Done?

**C-Peptide (Connecting peptide) is a substance produced by the beta cells in the pancreas when proinsulin splits apart and forms one molecule of C-peptide and one molecule of insulin. Since C-peptide and insulin are produced at the same rate, C-peptide is a useful marker of insulin production.** Unlike insulin which reduces sugar by helping its uptake by the cells for energy, the C-peptide does not reduce sugar levels in the blood.

C-Peptide is excreted by the kidney and its half-life is 3-4 times longer than insulin (4-6 minutes). Hence C-Peptide stays in the blood longer than insulin, and for every molecule of insulin secreted there is a C-Peptide. **As insulin is produced intermittently and disappears quickly form the blood, C-Peptide is a more robust method to assess the insulin producing capacity of the body.**


**How is it measured?**

**A blood test, after 8-12 hours of fasting,** will reveal C-Peptide levels in the blood. Simultaneously the blood sugar levels will also be measured. **Normal Range:** 0.8-3.1 ng/mL.

**Interpretation of values**

**High values indicate that high levels of insulin are produced** in the body to tackle high blood sugar levels and may be due to:

- Type 2 Diabetes (insulin resistance).
- Insulinoma (a tumor of the insulin-producing islet cells in the pancreas, causing low blood glucose levels).
- Excess intake of sulfonylureas (stimulate pancreas to secrete more insulin).
- Obesity (causes insulin resistance).

**Low values are associated with a low level of insulin production and may be due to:**

- Type 1 Diabetes Mellitus (destruction of beta cells of islets of Langerhans releases both insulin and C-peptide).
- Insulin therapy suppressing endogenous insulin production.
- Hypoglycemia (caused by insulin-like growth factor secreting tumors).

**Why is it done?**

For each molecule of insulin secreted there is a molecule of C-peptide; hence, it gives an indirect measure of the insulin secreted by the pancreas.

# Beyond The Pharmacodynamic Frontier

### Telmisartan & Olmesartan-based Combinations Improve Cardiovascular Biomarkers in Hypertensive Patients: RECENT EVIDENCE !

Jagodzinski A, et al. Clin Chem. 2017; 63(12): 1877-1885.

- Hypertension is associated with a high rate of cardiovascular events and mortality. Cardiovascular biomarkers can predict long-term risk.
- In 481 hypertensive patients randomized to either 80-mg telmisartan + 5-mg amlodipine or 40-mg olmesartan + 12.5-mg hydrochlorothiazide, **significant reductions were observed in BP and markers of cardiovascular risk** [high-sensitivity troponin I (hs-cTnI), high-sensitivity troponin T (hs-cTnT), B-type natriuretic peptide (BNP), and N-terminal-pro-BNP (NT-proBNP)] after 6 months.

### Metformin has Cardiovascular Benefits Unrelated to Antidiabetic Properties !

**Anti-Inflammatory Effects of Metformin Irrespective of Diabetes Status**

Cameron AR, et al. *Circ Res.* 2016; 119(5): 652-65.

- Metformin has cardiovascular benefits, but the underlying molecular mechanisms are poorly understood.
- Recent research has demonstrated that **metformin suppresses secretion of proinflammatory cytokines and inhibits tumor necrosis factor-α (TNF-α)-dependent expression of proinflammatory mediators (IL-6, 1L-1β). These effects were independent of its antihyperglycemic effects.**

### Metoprolol is Beneficial for Patients having Heart Failure with Preserved Ejection Fraction !

Mittal N, et al. Perspectives in Clinical Research. 2017; 8(3): 124-131.

- There is a lack of evidence-based therapies for the treatment of heart failure (HF) with preserved ejection fraction (HFpEF). Beta blockers may provide some benefit in HFpEF due to their proven role in HF with reduced ejection fraction.
- In a double-blind, 14-week pilot study, **metoprolol succinate improved the grading of HF (New York Heart Association class), echocardiographic parameters, exercise capacity and quality of life (QoL) parameters** in patients with HFpEF.
- No serious adverse events were observed.

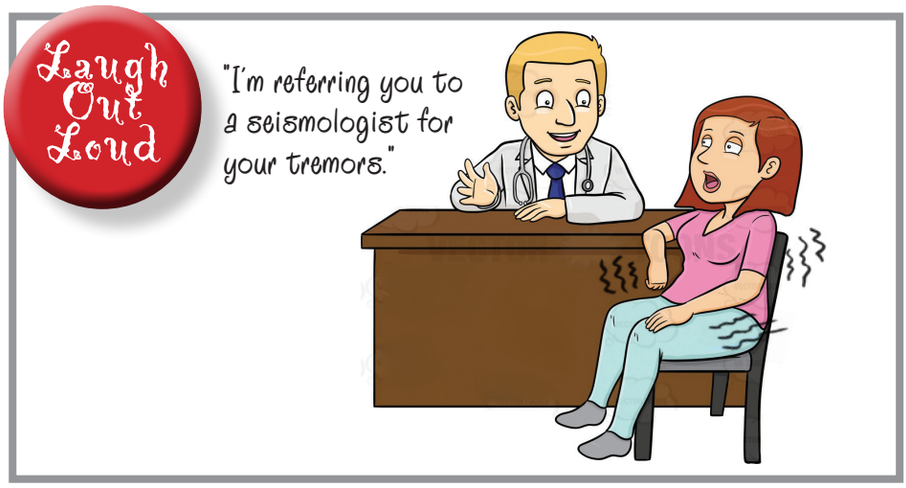
# Low Calcium may Raise Cardiac Arrest Risk by Two-Fold

Calcium is an essential mineral present in an abundance of foods, primarily dairy products such as milk and cheese. **Calcium is best known for its role in bone health, but a new study suggests that its role in heart health should not be overlooked. It was found that people with low levels of calcium in their blood may be at greater risk of sudden cardiac arrest (SCA).** SCA is when the heart suddenly stops beating due to a malfunction in the heart's electrical activity, which causes an irregular heartbeat, or arrhythmia.

Lead investigator Dr. Sumeet S. Chugh, of the Cedars-Sinai Heart Institute in Los Angeles, CA, and colleagues believe that their findings may pave the way for much-needed new diagnostic and treatment strategies for sudden cardiac arrest (SCA). The researchers recently reported their findings in the journal Mayo Clinic Proceedings.

The researchers gathered data from the Oregon Sudden Unexpected Death Study. They identified 267 people who experienced SCA between 2002 and 2015, alongside 445 healthy controls. **The results revealed that the risk of SCA was increased by 2.3-fold for participants who had the lowest blood calcium levels (under 8.95 milligrams per deciliter) compared with those who had the highest blood calcium levels (9.55 milligrams per deciliter).** These results remained after accounting for a number of possible confounding factors, including cardiovascular risk factors, medication use, and demographics.

**This is the first report to show that low serum calcium levels (even within the normal range of values) are independently associated with an increased risk of SCA in the general population.** Although the findings may not be ready for routine clinical use in patients at this time, they are **a step toward the goal of improving patient care/prognosis by better prediction of risk.**



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