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Medical Bulletin

Blue Cross Division

HYPERTENSION: COULD GUT BACTERIA PLAY A ROLE?

The gut microbiome and the host have evolved to exist in balance and there is an extensive crosstalk between the two systems in order to maintain homeostasis, including the regulation of blood pressure.

Researchers and epidemiological studies have long linked the gut dysbiosis with dysregulation of blood pressure.

A study in the journal Microbiome, analyzed the gut bacteria of 41 people with ideal blood pressure levels, 99 individuals with hypertension, and 56 people with prehypertension and it was found that in the participants with prehypertension or hypertension, there was a reduction in the diversity of gut bacteria.

HOW DO GUT BACTERIA AFFECT BLOOD PRESSURE?

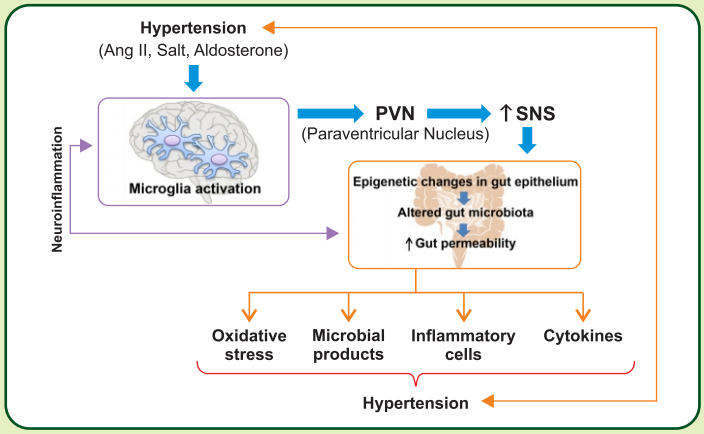
A newly identified interaction between the brain & the gut has been identified as a possible mechanism in the pathogenesis of hypertension.

Increased sympathetic activity to the gut could result in dysbiosis; increased gut permeability & inflammatory status lead to an imbalance in the gut content of short-chain fatty acids (SCFAs) producing bacteria & lipopolysaccharides in the plasma levels.

In addition to the anti-inflammatory actions of SCFAs viz. butyrate, acetate & propionate they also have anti-hypertensive properties.

The metabolic and structural microbial products, working together, elevate the sympathetic drive to the bone marrow and act as modulators to the pro-inflammatory cells. This increase contributes to an increase in the peripheral and central inflammation that could be a critical event for the establishment of hypertension also referred to as neurogenic hypertension.

The immune and sympathetic systems which exist as a bidirectional signaling between the brain and gut microbiota regulates the blood pressure. The modulation of this interaction between sympathetic nervous system & the immune system has made researchers suspect a link between hypertension & gut dysbiosis.



"Evidence is rapidly accumulating implicating gut dysbiosis in hypertension. However, we are far from understanding whether this is a cause or consequence of hypertension, and how to best translate this fundamental knowledge to advance the management of hypertension."

Source: Zubcevic J et al. Circ Res 2019, 125(1):104.

DYSMENORRHOEA

Dysmenorrhea is the medical term for menstrual cramps, which are caused by uterine contractions.

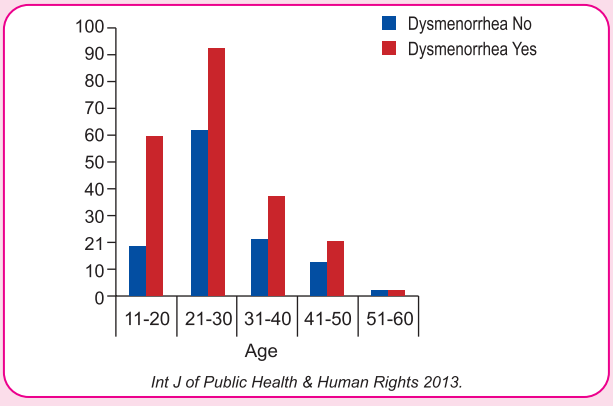
It can be either "Primary" or "Secondary".

The initial onset of primary dysmenorrhoea is usually 06 to 12 months after menarche, with the onset of ovulatory cycles.

Secondary dysmenorrhea can occur at any time after menarche, after the onset of an underlying causative condition.

PREVALENCE OF DYSMENORRHOEA IN INDIA

The epidemiology of primary dysmenorrhea is difficult to establish since it is a symptom that is perceived differently by different women. Dysmenorrhoea occurs at any age, affecting up to 90% of women of childbearing age to varying degrees.



Int J of Public Health & Human Rights 2013.

WHAT CAUSES DYSMENORRHOEA?

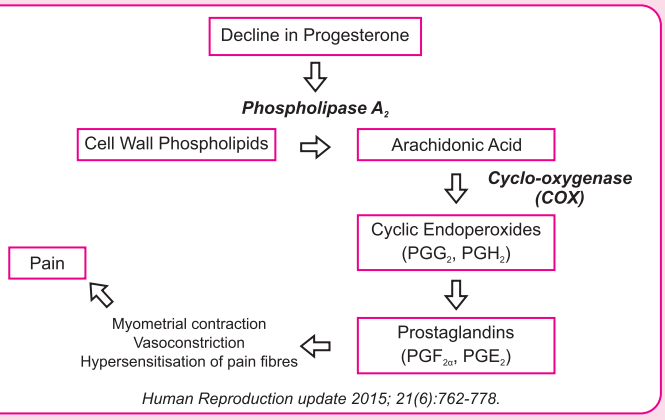
Primary dysmenorrhea occurs in the absence of any significant pathologic cause (idiopathic) whereas secondary dysmenorrhoea is a result of underlying pathological conditions.

Menstrual cramps are related to the levels of prostaglandins (PGs) which stimulate the uterine muscle to contract. PGs are

ubiquitously distributed and are a common component of cell membrane phospholipids. They are derived from long-chain polyunsaturated fatty acids (PUFAs), such as arachidonic acid, with the help of the enzyme, cyclooxygenase (COX).

These PGs rise and fall during the menstrual cycle and hence, most symptoms of dysmenorrhoea can be explained by the action of uterine PGs, particularly $PGF_{2\alpha}$.

During endometrial sloughing, the disintegrating endometrial cells release $PGF_{2\alpha}$ as menstruation begins. $PGF_{2\alpha}$ stimulates myometrial contractions ischemia and sensitization of nerve endings. The levels of $PGF_{2\alpha}$ are highest during the first two days of menses, when symptoms are at their peak.



Human Reproduction update 2015; 21(6):762-778.

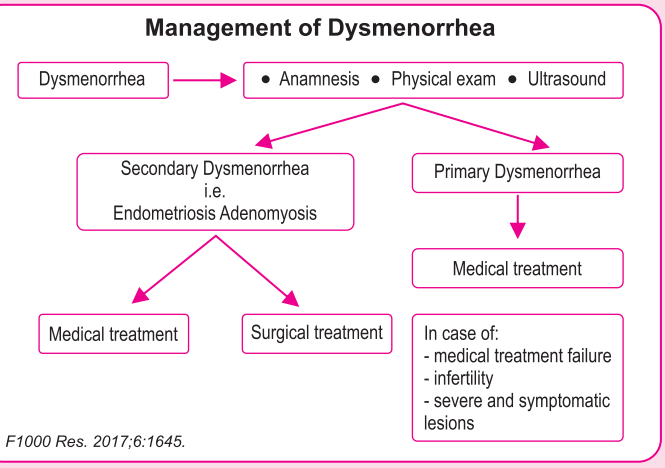
Women who have more severe dysmenorrhea have higher levels of $PGF_{2\alpha}$ in their menstrual fluid. These higher levels of PGs make the uterus contract too strongly which can press against nearby blood vessels, cutting off the supply of oxygen to the muscle tissue of the uterus, causing uterine ischemia and resulting in pain.

What are the symptoms of Dysmenorrhea?

- Pain or cramping in the lower abdomen
- Lower back pain, pain in the legs
- Nausea, vomiting, diarrhea, bloating
- Headaches, dizziness, fainting spells
- Fatigue and malaise

How can Dysmenorrhea be managed effectively?

Dysmenorrhoea, especially when it is severe, is associated with restriction of activities and absence from school or work, affecting substantially their quality of life and general wellbeing.



F1000 Res. 2017;6:1645.

Investigations and diagnosis using a focused history, physical examination & information about the onset, location, duration, & characteristics of pain, plus any aggravating or relieving factors helps in diagnosis of dysmenorrhea.

Medical management

The primary aim in the management is to relieve the "menstrual cramps" or spasms which are an important symptom of dysmenorrhea.

PAIN

The pain associated with dysmenorrhoea can be of various forms, the most obvious being abdominal pain. However, it can also spread to lower back, thighs and legs. The pain can be gripping or feel like a constant ache or a combination of both.

(NSAIDs) block the COX enzymes and reduce prostaglandins throughout the body. As a consequence, ongoing inflammations, and pain, are reduced.

Depending on the selectivity of the COX enzyme, they are classified as:

Non-selective Cox inhibitors (<5-fold Cox-2 selective)	• Aceclofenac • Diclofenac	• Ibuprofen • Mefenamic acid
Preferential' Cox-2 inhibitors (50-fold Cox-2 selective)	• Etodolac • Meloxicam	• Nabumetone • Nimesulide
Cox-2 selective inhibitors (>50-fold Cox-2 selective)	• Celecoxib • Etoricoxib	• Rofecoxib • Lumiracoxib

SPASM

A spasm is a sudden involuntary contraction of a muscle, or a group of muscles for an extended period of time.

Spasms during dysmenorrhea are particularly referred to as menstrual cramps and occur due to contractions in the uterus, which is basically a smooth muscle.

Contractions during menses are usually normal, however severe and painful contractions is a symptom of dysmenorrhea which are usually excessive contractions of the uterus.

Spasms can be managed by the use of antispasmodics.

Antispasmodics are a broad group of medicines that act on neurotransmitters and proinflammatory cytokinins and by blocking their action they prevent impulses from the parasympathetic nervous system from reaching smooth muscle and causing contractions, cramps or spasms.

They are also classified on the basis of their mode of action:

Anti-muscarinic	They block the cholinergic transmission at parasympathetic nerve ending and cause smooth muscles to relax. ***Hyoscine.***
Direct smooth muscle relaxants	They have a direct effect on the smooth muscle activity. ***Drotaverine; Camylofin.***
Both	They have an anticholinergic as well as direct smooth muscle action. ***Dicyclomine.***

MEFENAMIC ACID

- Inhibits cycloxygenase (COX) enzyme which is responsible for formation of PGs.
- It also blocks the EP receptors to prevent the effects of preformed prostaglandins.
- Mefenamic acid produces a strong analgesic effect by inhibiting both, the synthesis & response to Pgs.

DICYCLOMINE

- Dual Mechanism: Anti-cholinergic agent & Spasmolytic.
- Relieves spasm of uterus & other smooth muscles (such as intestine, biliary & ureteric tract).
- Anticholinergic effect at the acetylcholine-receptor sites (muscarinic-M_1 receptor) offers direct spasmolytic effect upon the smooth muscles of uterus.

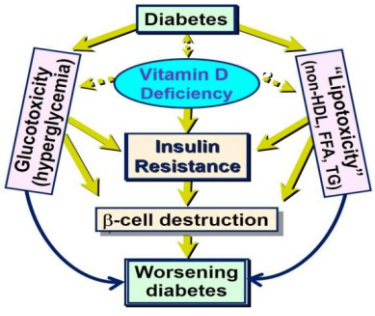
NEED FOR COMBINATION

- Combination therapy offers comprehensive pain relief from spasmodic dysmenorrhoea/menstrual cramps.
- This is because, mefenamic acid inhibits prostaglandins synthesis and dicyclomine reduces spasm of uterus.
- Moreover, a fixed dose combination of mefenamic acid with dicyclomine was found to be highly effective, well tolerated and safe in reducing dysmenorrhoea pain and in restoring the functional ability of the patients.

References: Alsaleem MA. J Family Med Prim Care 2018, 7(4): 769-774; Bernardi M et al. F1000 Res 2017, 6: 1645; Omidvar S et al.Global J Health Sci 2016, 8(8): 135-144; my.clevelandclinic.org/health/dis/4148-dysmenorrhea.

VITAMIN D AND DIABETES

Traditionally, Vitamin D has been considered almost exclusively for its role in calcium homeostasis, but with the discovery of Vitamin D Receptor (VDR) and its presence in various tissues & cells in the body, its role has been widely explored in various conditions, diabetes being one of them.



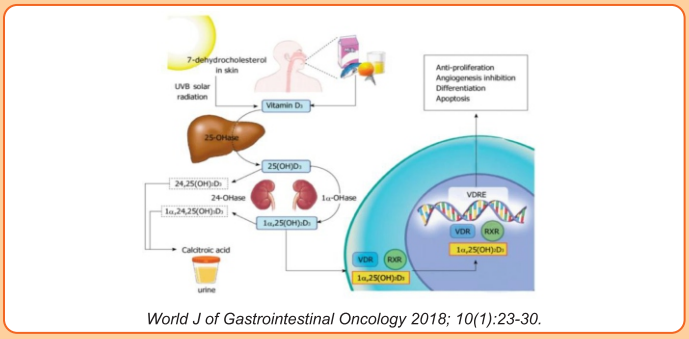
J of steroid Biochem & Mol Biology 2018; 175:177-189.

Research in the past few years has linked Vitamin D deficiency to the onset of diabetes as it has been discovered that a remarkable number of cellular processes are maintained by Vitamin D. Thus, when Vitamin D is deficient, many of these processes begin to decline and this sets the stage for the onset of Diabetes.

How does Vitamin D deficiency contribute to T2DM?

Type 2 Diabetes (T2DM) is initiated by the onset of insulin resistance which is overcome by the β cells by releasing more insulin, but as the hyperactivity increases, the β cells experience Ca^+ and ROS signaling resulting in cell death leading to exhaustion and β cells dysfunction.

Vitamin D deficiency contributes to both, the initial insulin resistance as well as to the subsequent onset of diabetes caused by the β cell death.



World J of Gastrointestinal Oncology 2018; 10(1):23-30.

How is Vitamin D implicated in the pathogenesis of T2DM?

VITAMIN D AND VDR

VDR in the pancreatic β cells play an important role in the progression of T2DM.

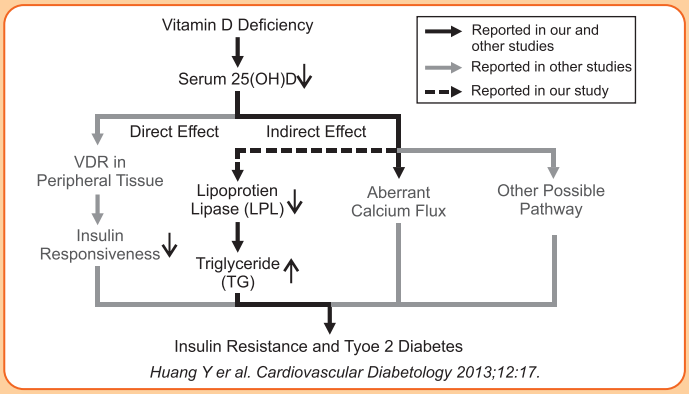
Cells lacking a functional VDR shows impaired insulin secretion, following glucose load, which is associated with impaired insulin synthesis by the β cells.

Vitamin D appears to stimulate the expression of insulin receptors, which in turn affects the insulin sensitivity by entering the insulin responsive cells and interacting with the VDR, activating the VDR-Retinoic acid X receptor complex which binds to a Vitamin D response element found in human insulin receptor gene promoter region, resulting in enhanced activation of insulin receptor gene, thus increasing the total number of insulin receptors without altering their affinity.

VITAMIN D AND CALCIUM INFLUX

The insulin secretion is a calcium dependent process and is regulated by the Ca^+ concentration and flux through the β cells. Vitamin D regulates the intracellular Ca+, and calbidin, a systolic calcium binding protein found in pancreatic β cells which acts as a modulator of depolarization.

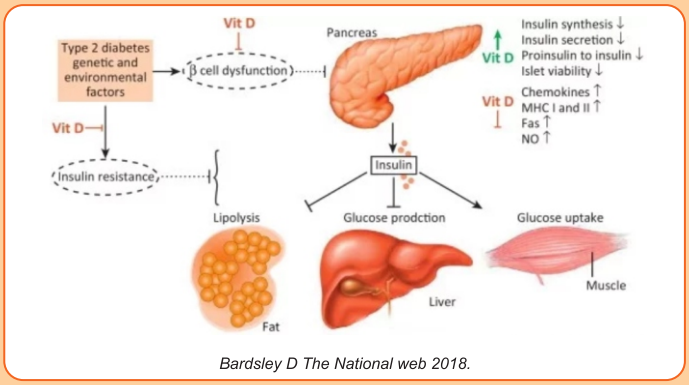
PTH, which has its concentration regulated by Vitamin D, is also associated with insulin synthesis and secretion in the pancreas.



Huang Y er al. Cardiovascular Diabetology 2013;12:17.

VITAMIN D AND INFLAMMATION

Vitamin D helps in inhibiting the surface expression of the MHC class II complex and co-stimulatory molecules, and the production of the pro-inflammatory cytokines thereby dampening the type 2 DM-associated inflammation in the pancreas.



Bardsley D The National web 2018.

Effect of vitamin D on pathophysiology in (T2D)

Thus, biologically active vitamin D can reduce β cell dysfunction by restoring impaired insulin production and islet viability.

VITAMIN D & EPIGENETIC ALTERATIONS

Vitamin D plays a significant role in maintaining the epigenome.

Epigenetic alterations are a feature of diabetes, by which many diabetes related genes are inactivated by hypermethylation. Vitamin D helps to prevent this hypermethylation by expressing the DNA demethylases that prevent hypermethylation of multiple gene promoter regions of many diabetes related genes.

Some of the clinical trials findings are presented as follows:

- In a double-blind, randomized, placebo-controlled clinical trial on 127 patients with stable (HbA1C <= 7.5%) diabetes, managed with lifestyle only or on lifestyle modification and metformin, it was observed that administration of 4000IU of Vitamin D3(Cholecalciferol) for 48 weeks or placebo, Vitamin D supplementation reduced the HbA1C as compared to placebo at week 24.
- In a double-blind, placebo-controlled, randomized trial on 162 adults with prediabetes and Vitamin D deficiency, high doses of Vitamin D improved insulin sensitivity and decreased the progression towards diabetes.
- In a randomized clinical trial, 28 patients with T2DM received 4000 IU of Vitamin D and 30 patients received placebo for 2 months. It was observed that there was a significant decrease in HbA1C and the insulin concentration in the supplemented group, concluding that Vitamin D supplementation has a beneficial effect on glucose homeostasis as well as insulin sensitivity in patients with T2DM.

In conclusion it has been scientifically seen that the significance of Vitamin D supplementation in patients with diabetes is significantly beneficial and that supplemental vitamin D can be effectively used to manage diabetes as well as delay the progression of prediabetes to diabetes.

Source: Niroomand M et al. Diabetes Res clin Prac 2019; 148: 1-9.; Angellotti E et al. J Endocrine Soc 2018; 2(4): 310-321; Berridge MJ. Biochem J 2017; 474 (8): 1321-1332; Nakashima A et al. World J Diabetes 2016; 7(5): 89-100; Yousefi RE et al. Iran J Public Health 2014; 43(2): 1651-1656; Mitri J & Pittas AG. Endrocrinol Metab Clin North Am 2014; 43(1): 205-232.; Christakos S et al. Ann N Y Acad Sci 2013; 1287: 45-58.

FOOD, DIET & INFLAMMATION

What does an anti-inflammatory diet do?

An immune system becomes activated when body recognizes anything that is foreign - such as an invading microbe, plant pollen, or chemical. This often triggers a process called inflammation.

The health risks of inflammatory foods

Some of the foods that have been associated with an increased risk for chronic diseases such as type 2 diabetes and heart disease, are also associated with excess inflammation. It's not surprising, since inflammation is an important underlying mechanism for the development of these chronic metabolic disorders.

Unhealthy foods contribute to weight gain, which itself is a risk factor for inflammation.

Choosing the right anti-inflammatory foods reduces the risk of illness, whereas, the wrong foods may accelerate the inflammatory disease process. To reduce levels of inflammation, one should aim for an overall healthy diet. For this, consider diet, which is high in fruits, vegetables, nuts, whole grains, fish, and healthy oils.

Benefits of anti-inflammatory foods

- Fruits and vegetables such as blueberries, apples, and leafy greens, those are high in natural antioxidants & polyphenols, which protects from oxidation and inflammation.
- Nuts also reduce markers of inflammation and lowers risk of cardiovascular disease and diabetes.
- Coffee, which contains polyphenols & other anti-inflammatory compounds, may protect against inflammation, as well.

In addition to lowering inflammation, a more natural, less processed foods can have noticeable effects on physical and emotional health.
A healthy diet is beneficial not only for reducing the risk of chronic diseases, but also for improving mood and overall quality of life.

Source: health.harvard.edu

For More Information: **Dr. Prabhu Kasture** (MD, DPH), GM- Medical Services. **Call:** 022 66638043 **e-mail:** prabhu.k@bluecrosslabs.com **Correspond:** Blue Cross Laboratories Pvt Ltd. Peninsula Chambers, Ganpatrao Kadam Marg, Lower Parel, Mumbai 400 013

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