QUARTER 2, 2022 | VOLUME 10 | NUMBER 3

BLUE CROSS Medical Bulletin

BC Division of Blue Cross Laboratories Pvt Ltd.

# COMBINATION THERAPY WITH DIABIZ (DAPAGLIFLOZIN)

Type 2 diabetes is a progressive disease and most patients ultimately require two or more anti-diabetes drugs in addition to lifestyle changes to maintain glycemic control.

Current consensus and guidelines recommend the use of metformin as the first-line drug in the management of type 2 diabetes in most patients. However, when glycemic control cannot be maintained with metformin alone, sequential stepwise addition of other anti-diabetic drugs is recommended.

Agents such as thiazolidinediones or sulfonylureas have typically been added to metformin therapy and although effective in reducing the HbA1c, these drugs have been associated with certain adverse effects such as weight gain and in case of sulfonylureas, hypoglycemia.

***SGLT2 inhibitors such as dapagliflozin are a class of anti-diabetic drugs for management of type 2 diabetes that effectively improve glycemic control by increasing the renal excretion of excess glucose.***

Clinical trials have shown dapagliflozin to be well tolerated with additional benefits of weight loss, reduction in blood pressure and a low risk of hypoglycemia. Dapagliflozin add-on therapy has been researched as a promising new treatment option for a wide range of patients with type 2 diabetes.

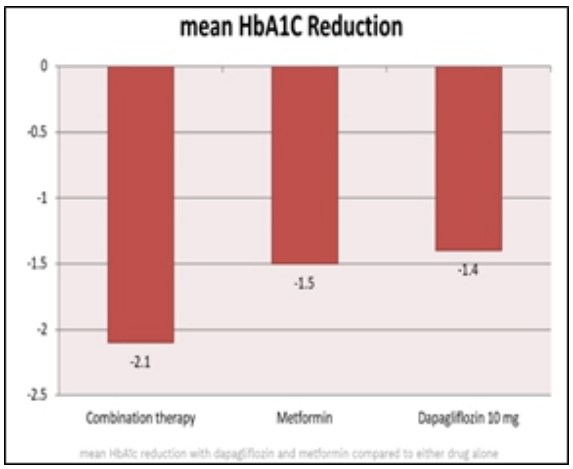
***Initiating simultaneous combination therapy at early stage of the disease rather than a sequential stepwise approach may help in earlier achievement of glycemic goals, durable efficacy and better preservation of cell function as compared to gradual treatment intensification.***

## COMBINATION THERAPY

Studies have shown that dapagliflozin used in combination either as dual therapy, triple therapy and quadruple therapy with various other oral anti-diabetic agents has been safe and effective in maintaining desired glycaemic levels along with additional benefits of weight loss and modest blood pressure control.

## DUAL THERAPY

When added to a usual background regimen in patients with advanced type 2 diabetes along with pre-existing CVD, dapagliflozin improves glycaemic control without an increase in hypoglycaemic risk, promotes weight loss, and has good tolerability.




Dapagliflozin has been shown to be safe and effective with most other classes of oral anti-diabetic agents such as biguanides like metformin, sulfonylureas like glimepiride, DPP-4 inhibitors like sitagliptin and thiazolidinediones like pioglitazone.

*Dapagliflozin, when studied in dual therapy with various other oral hypoglycaemic agents, the highest reduction in HbA1c was observed when it was combined with metformin as compared to when combined with other oral hypoglycaemic agents.*

In addition, dapagliflozin when added to insulin has been shown to reduce the dosage of insulin intake as well as lower the incidence of hypoglycaemia. Since dapagliflozin acts independently of insulin, it seems reasonable to co-administer it with insulin regimes to improve glycaemic control.

Studies have established the concept that SGLT2 inhibition improves glycaemic control and weight in patients with diabetes that is poorly controlled with high insulin doses and oral insulin sensitizer therapy. These results further suggest the hypothesis that this therapeutic approach may lend itself to reducing the weight gain that otherwise might occur when insulin therapy is intensified.

**TRIPLE THERAPY**

***Dapagliflozin in a triple drug combination with DPP-4 inhibitors like saxagliptin, sulfonylureas as well as with insulin*** has shown that the addition of dapagliflozin to an existing regimen of metformin with either a DPP-4 inhibitor or sulfonylurea and even insulin had better effects in reducing HbA1c, body weight and blood pressure.

**QUADRUPLE THERAPY**

A recent long-term study of dapagliflozin used in addition to an existing triple drug regimen has shown a significant reduction in the HbA1c and in the fasting plasma glucose levels with a good tolerance to the combination, thus demonstrating a positive long-term effect on glycaemic control.

***Dapagliflozin used as monotherapy or as add-on treatment in type 2 diabetes patients significantly decreases HbA1c and FPG levels achieving adequate glycaemic control and significantly reduces body weight, blood pressure with a low risk of hypoglycaemia.***

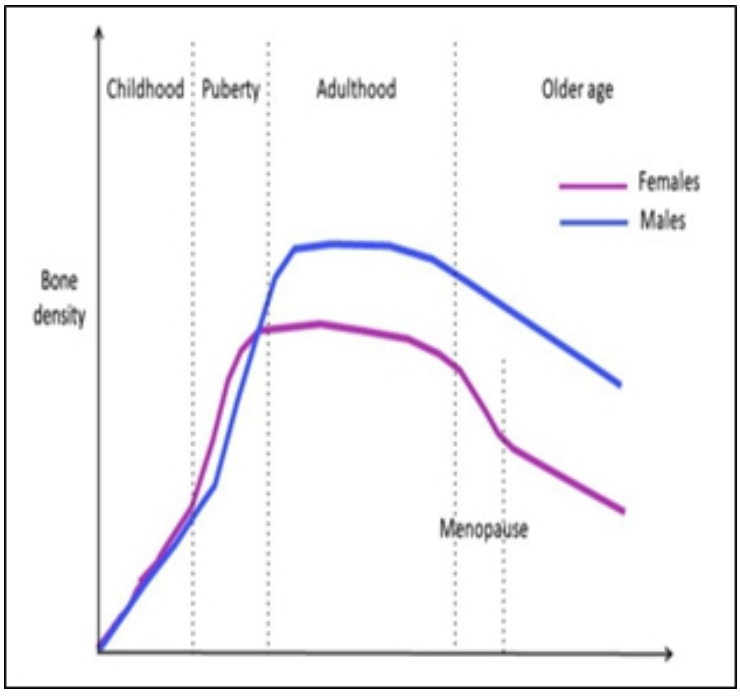
*Source: Yacoub T et al. Postgrad Med 2016; 128(1): 124-136; Kaku K et al. Diabetes Ther 2014; 5: 415-433; Handelsman Y et al. Diabetes Obes Metab 2019; 21: 883-892; Ku EJ et al. Diabetes Res Clin Pract 2021; 182: 109123.*

## ROLE OF VEBA PLUS (CALCIUM CITRATE MALATE) IN POST MENOPAUSAL WOMEN

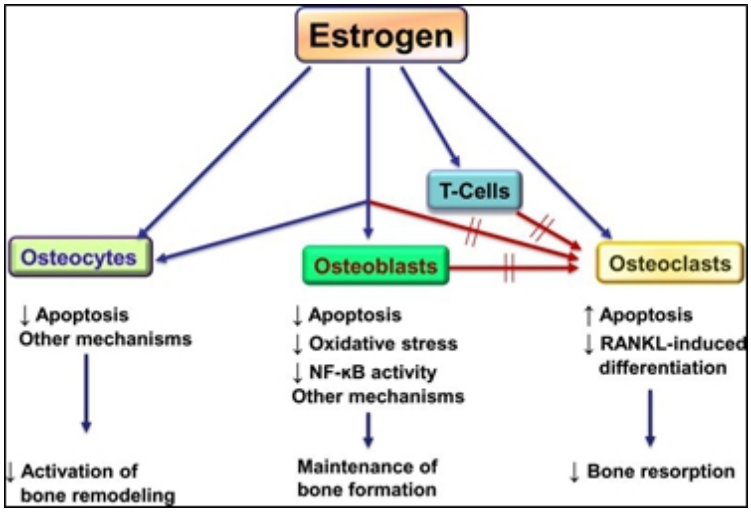
Calcium is the most abundant mineral in the human body with about 99% of the stores contained in the skeleton. The calcium requirements for skeletal maintenance fluctuate throughout a woman's life cycle with calcium requirements remaining relatively stable until menopause and increasing thereafter when the bone resorption rate increases in association with decreased ovarian estrogen production.

The calcium needs also rise because of the decreased efficiency in utilization of dietary calcium which is mainly due to estrogen related shifts in intestinal calcium absorption and renal conservation.

The amount of calcium needed is also affected by the decrease in intestinal absorption that occurs with age.



## OSTEOPOROSIS IN POST MENOPAUSAL WOMEN




Postmenopausal women are susceptible to primary osteoporosis because osteoporosis is closely related to estrogen deficiency.

During the menopausal transition period, the drop of estrogen leads to more bone resorption than formation, resulting in osteoporosis.

At menopause the normal bone turnover cycle is impaired by estrogen deficiency. This may be due to the presence of estrogen receptors in osteoclast progenitor cells and multi-nucleated osteoclasts.

***The osteoclastic resorption activity increases while the osteoblastic activity decreases.*** As a result, the amount of bone resorbed exceeds the amount deposited, which leads to a net loss of bone.

***A decline in the circulating levels of estradiol is the predominant factor influencing the accelerated bone loss and increased remodelling activity associated with menopause.***

A major health threat for osteoporosis are osteoporotic fractures which occur at the sites with low bone mass density (BMD) such as mainly the spine and the hip. Up to 90% of all spine and hip fractures in older women can be attributed to osteoporosis.

***Bone loss at the spine begins about 1.5 years before the last menstrual period and progresses at the rate of approximately 3% per year for about 5 years amounting to a total BMD loss of 15%.***

***Similarly, the bone loss at the hip occurs at a rate of 0.5% per year before and after menopause and sustains an additional loss of 5-7% across the menopause transition period.***

There are two phases of bone loss in women:

- The first phase occurs predominantly in trabecular bone (which is the spongy interior part of the vertebra and long bones and accounts for and 25% of the calcium in the female vertebral column) and starting at menopause. It results from estrogen deficiency, and leads to a disproportionate increase in bone resorption as compared with formation.
- After 4-8 years, the second phase exhibits a persistent, slower loss of both trabecular and cortical bone, and is mainly attributed to reduced bone formation. This is age related bone loss, which is the only phase that also happens in men.

| Postmenopausal Osteoporosis (Type I) | Senile Osteoporosis (Type II) |
|---|---|
| Occurs in 50–65 year-old women | Occurs in men and women > 70 years of age |
| Predominant increase of osteoclastic activity | Predominant decrease in osteoblastic activity |
| Characterized by an accelerated phase of hypoestrogenism-related bone loss | Represents bone loss associated with aging |
| More significant trabecular bone loss | More significant cortical bone loss |
| The predominant fractures are vertebral bodies and distal forearm | The predominant fractures are hip, wrist, vertebral |

***The primary goal for the approach to post-menopausal osteoporosis is to prevent fractures by slowing or preventing bone loss.***

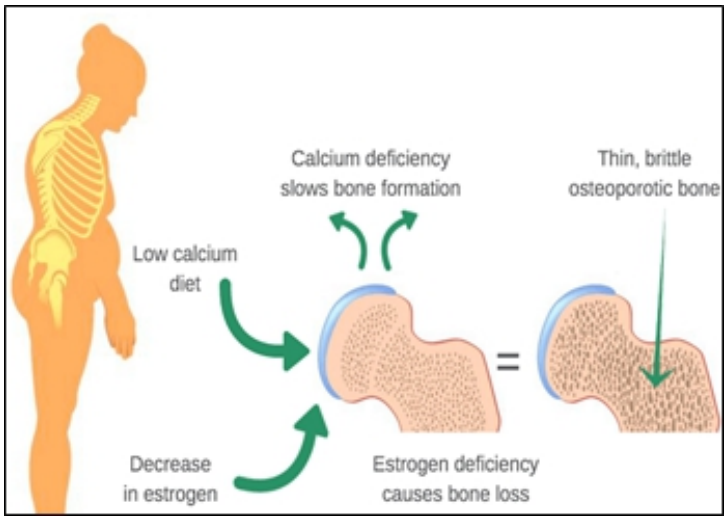
## PREVALENCE OF POST MENOPAUSAL OSTEOPOROSIS IN INDIAN WOMEN

Currently 200 million people suffer from osteoporosis worldwide suffer from osteoporosis. Approximately 30% of all post-menopausal women have osteoporosis in the United States and Europe. ***In India, the prevalence of osteoporosis in post-menopausal women has shown to vary from 25-62%.***

The reason for this extensive range is due to the lack of awareness about osteoporosis in India, with surveys indicating that only 10-15% of Indians are aware of the disease.

## CALCIUM CITRATE MALATE FOR POST MENOPAUSAL OSTEOPOROTIC WOMEN

Calcium citrate malate (CCM) is a water-soluble calcium salt with a high aqueous solubility, enhanced absorption and enhanced bioavailability. The structure of CCM is such that it increases the dissolution in the stomach 6-9 times as compared to calcium citrate even when taken with food. The absorption of CCM in the body is approximately ***42% as compared to 22% from calcium carbonate.*** This enhanced absorption compensates for lower elemental calcium in CCM as well as lower dosing as compared to calcium carbonate.




Post-menopausal women, with calcium intakes lesser than 400 mg/d exhibit a greater rate of calcium loss from the spine as compared to women with higher intake of calcium. ***A placebo-controlled study on post-menopausal women comparing CCM and calcium carbonate over a period of 2 years showed that the supplementation of CCM was more successful than supplementation with calcium carbonate and CCM mainly prevented bone loss from the spine.***

Preclinical studies have shown that supplementation with CCM has resulted in the formation of 23-25% trabecular bone at 4 weeks and 44-47% at 12 weeks as compared to calcium carbonate concluding that CCM is more bioavailable than calcium carbonate.

***Since the first phase of post-menopausal osteoporosis begins with the loss of trabecular bones, mainly affecting the vertebrae and the spine, the supplementation with CCM would be beneficial in managing the same.***

## CONCLUSION

***It can be suggested that post-menopausal women with an inadequate dietary calcium intake, expand their calcium intakes by adding supplemental calcium in order to restrict bone loss.***

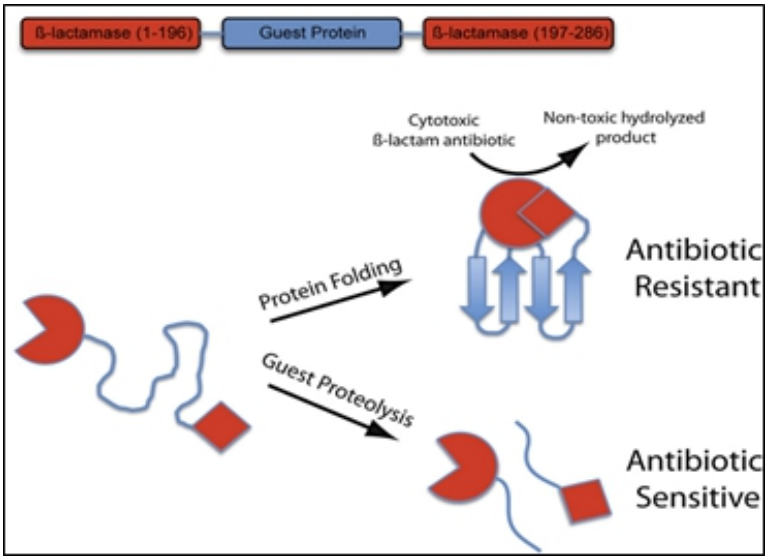
***Considering the facts, CCM can be used as a preferable supplement due to its higher bioavailability and its beneficial effects on spinal bone loss as compared to calcium carbonate.***

*Source: Menopause: The J of North American Menopause Society 2006; 13(6): 862-877; Xaia Ji M & Qu Y. Chronic Dis Transl Med 2015; 1(1): 9-13; Nottestad SY et al. J Bone Miner Res 1987; 2(3): 221-229; Rajan R et al. Current Medical Issues 2020; 18(2): 98-104; Bhadada SK et al. Archives of Osteoporosis 2021; 16(102); Kochanowski BA. J Nutr 1990; 120(8): 876-881.*

## REVERSING ANTIBIOTIC RESISTANCE

Antimicrobial resistant (AMR) pathogens are projected to kill 10 million people annually by the year 2050 as against 700,000 per year currently with India becoming one of the worst affected countries. Bacteria are becoming increasingly resistant to existing antibiotics, and researchers have struggled to identify new bacteria-fighting drugs, leaving the world vulnerable to deadly superbugs.

A team of researchers have found a new way to impair antibiotic resistance in bacteria that cause human disease and are responsible for the majority of harm caused by the resistant infections.




Researchers have made the bacteria vulnerable again to antibiotics by inhibiting a particular protein that drives the formation of resistance capabilities within the bacteria.Antibiotic resistant bacteria have a host of different proteins that neutralize antibiotics. To function properly, these resistance proteins must be folded into the right shapes.

The researchers have discovered yet another protein, called **DsbA,** that helps fold the resistance proteins into required shapes.

The goal is to combine a **DsbA** inhibitor with existing antibiotics to restore the drugs' ability to kill the bacteria and as it targets the machinery that helps assemble antibiotic-resistance proteins in dangerous bacteria, the approach would render several types of proteins critical for resistance ineffective, by preventing their ability to fold or create disulfide bonds.

***Findings have shown that by targeting disulfide bond formation and protein folding, it is possible to reverse antibiotic resistance across several major pathogens and resistance mechanisms.***

***Since the discovery of new antibiotics is challenging, it is crucial to develop ways to prolong the lifespan of existing antimicrobials and for this development of clinically useful DsbA inhibitors in the future could offer a new way to treat resistant infections using currently available antibiotics.***

*Source:https://www.sciencedaily.com/releases/2022/02/220222135331.htm;https://www.imperial.ac.uk/news/234060/scientists-discover-approach-fighting-antibiotic-resistance/*

Dr. Prabhu Kasture (MD, DPH)
Dy. Director Medical Services & Pharmacovigilance



PHONE NO.: 022-666638043
EMAIL: prabhu.k@bluecrosslabs.com
Correspond: Blue Cross Laboratories Pvt. Ltd. (Peninsula Corporate Park, Peninsula Chambers, Ganpatro Kadam Marg, Lower Parel, Mumbai-400013