Osteoporosis is one of the most prevalent health problems in Hong Kong. It has been estimated that one third of postmenopausal women and 20% of older men in Hong Kong suffer from osteoporosis. Moreover, the incidence of hip fracture, which is the major complication of osteoporosis, increased by 2-3 folds in the Hong Kong population over the last 3 decades.

Osteoporosis results when there is uncoupling of the functions of the Bone Metabolic Unit i.e. the activity of the osteoclasts exceeds that of the osteoblasts. Antiresorptive drugs, including the bisphosphonates and raloxifene, have been found to be efficacious in suppressing bone loss in osteoporotic patients. On the other hand, teriparatide injections could enhance bone formation and increase bone mass. A new compound-strontium ranelate-was recently shown to have both antiresorptive and bone forming effects. This could be a promising new breakthrough in the clinical management of osteoporosis.

The mechanism of action of strontium ranelate

The anti-resorbing and bone-forming effects of strontium ranelate have been demonstrated in several animal studies. In mouse calvaria cultures, strontium ranelate inhibits bone resorption by around 30%. Additionally, strontium ranelate decreases osteoclast activity by about 30%, as measured by pit assay in isolated rat cells. Further studies indicate that strontium ranelate has positive effects on bone formation in vitro. In rat calvaria organ and cell cultures, strontium ranelate has been shown to enhance the replication of preosteoblastic cells, as well as the activity of funcational cells and bone matrix synthesis.

The mechanisms of action of strontium are not fully understood, but several mechanisms are possible. Firstly, strontium was found to activate the calcium sensing receptor in some cell types, resulting in activation of inositol triphosphate production and mitogen-activated protein kinase signalling. Strontium was also found to induce cyclooxygenase-2 expression and prostaglandin E2 production.

Effects of strontium ranelate on bone mass

The in vitro effects of strontium ranelate are also observed in vivo. In adult mice and rats, treatment by strontium ranelate causes an increased bone mass at the vertebra and femur. In normal adult monkeys, strontium ranelate caused a decrease in bone resorption and increased bone mineralisation in alveolar bone.

Strontium ranelate was also found to be effective in preventing bone loss in osteoporotic animal models. In ovariectomized rats, strontium ranelate prevented bone loss induced by estrogen deficiency, as a result of decreased bone resorption. In another study where bone loss was induced by immobilisation, strontium ranelate prevented the increased bone resorption and trabecular bone loss.

Clinical trial results on strontium ranelate

According to the principles of evidence based medicine, the results of randomised controlled clinical trials should be carefully scrutinised before drugs are recommended for use in clinical settings. The results of randomised controlled clinical trials confirm the effectiveness of strontium ranelate in increasing bone mass in osteoporotic women.

In the first clinical trial, a significant increase of 7.3% per annum was observed in women given 2g of strontium ranelate per day. Moreover, the percentage of patients with new vertebral fracture was reduced by 44% in the second year of the study.

The antifracture efficacy of strontium ranelate was assessed in 2 large randomised controlled clinical trials, the Spinal Osteoporosis Therapeutic Intervention (SOTI) Trial, and the Treatment of Peripheral Osteoporosis Study (TROPOS). The SOTI Trial involved 1649 postmenopausal women with osteoporosis and at least one vertebral fracture. Oral strontium ranelate (2g daily), or placebo, was given for 3 years. New vertebral fractures occurred in fewer patients in the strontium ranelate group than in the placebo group, with a risk reduction of 49% in the first year of treatment and 41 % in the 3-year period (relative risk 0.59, 95% CI 0.48-0.73). At the end of 3 years, the bone mineral density at the lumbar spine, adjusted for strontium content, showed an increase of 6.8% over the baseline.

In the TROPOS study, 5091 postmenopausal women with osteoporosis were recruited. In the entire sample, relative risk was reduced by 16% for all nonvertebral fractures and 19% for major fragility fractures. In the high risk subgroup for hip fracture, the Relative Risk Reduction was 36%. The average difference between the strontium treated group and the placebo group at 3 years was...
8.2% at the femoral neck and 9.8% at the total hip. A 50% adjustment is recommended for the effects of strontium content on dual X-ray densitometry measurements.

In both SOTI and TROPOS, strontium ranelate appeared to be well-tolerated, the most common side effects were nausea and diarrhea, which disappeared after a few months.

Two clinical cases below illustrate the potential indications for using strontium:

**Case 1**
Mrs Cheung is a 64 years old lady with recently diagnosed established osteoporosis (According to Dual X Ray Densitometry, T score at the lumbar spine was -2.8 and T score at the hip was -2.5). She has had 3 episodes of upper gastrointestinal bleeding, resulting from gastric ulcer, in the last 3 years.

**Comments**
Strontium ranelate may be useful to treat her osteoporosis, for bisphosphonates are contraindicated due to the history of GI bleeding.

**Case 2**
Mrs Lee is a 59 years old lady with established osteoporosis diagnosed 2 years ago. According to dual X-Ray densitometry, her BMD was -3 at the spine and -2.9 at the hip at the time of the diagnosis. She was prescribed a bisphosphonate by her physician. Her BMD was -3.3 at the spine and -2.7 at the hip, at 12 months after drug treatment was commenced. A repeat BMD at 24 months showed a T score of -3.5 at the spine and -2.9 at the hip.

**Comments**
Sequential decrease in BMD may suggest that the patient is not responding to bisphosphonates. Strontium ranelate could be considered in this situation.

**Conclusion**
Strontium ranelate is a unique agent with both anti-resorbing and bone-forming effects. Although the exact molecular and cellular mechanisms for its mode of action remain to be established, it is useful in the treatment of osteoporotic patients.

**References**