

Significant contributions Dr Ravinder Goswami in Medical-Sciences (Endocrinology) based on the work done in India

Dr. Ravinder Goswami has carried out significant clinical research in **hypocalcemic endocrine diseases in our country**. His research work has provided lead information on prevalence and causes of vitamin-D deficiency in India despite abundance of sunshine, predisposition and cause of osteomalacia and rickets in females, assessment of bio-adaptation at vitamin-D receptor level and an easy and practical vitamin-D supplementation schedule in India. For his in-depth studies in the another hypocalcemic disorder i.e. idiopathic hypoparathyroidism, he as a clinician endocrinologist has carried out bedside to bench work resulting in unraveling the pathogenesis of disease at molecular level and identification of new clinical symptoms and signs of the disease.

These lead studies of the nominee have applied importance and are of immediate relevance from the public health point of view in our country. Most of the work of the nominee is published in the prestigious high impact peer reviewed international and national journals of Endocrine and Nutrition specialty and as summarized below.

(A) Awareness, prevalence, cause of hypovitaminosis-D and its functional significance

Disorders such as osteomalacia, rickets and osteoporosis are widely prevalent in India. The role of vitamin-D deficiency in the etio-pathogenesis was not established. Vitamin-D deficiency as such was considered to be rare in India due to its sunny environment. For the first time, using a novel study design involving healthy subjects with different bone mineral characteristics, the nominee has scientifically documented the existence of significantly deficient levels of 25(OH)D in up to 90% of apparently healthy indoor Indians related to their skin melanin and/or poor sunshine exposure (**Am J Clin Nutr 2000;72: 472-75, impact factor 6.6**). The nominee has further shown the functional relevance of hypovitaminosis-D in Indians in terms of high circulating levels of serum parathyroid hormone and decreased bone mineral density. He has also reported on the role of vitamin-D receptor genotypes in determining osteoporosis in hypovitaminotic-D states (**Clin Endocrinol 2006; 64:405-9, impact factor 3.4 and Am J Clin Nutr 2006; 83:1410-8**). Recently, Dr. R. Goswami carried out a large community based survey in a cohort of 642 school children and teachers in urban Delhi and showed continued wide prevalence of vitamin-D deficiency which predisposes to the thyroid autoimmunity (**Br J Nutr 2009**).

Nominee's work on vitamin-D deficiency has triggered a number of studies in India and abroad (Please see the citation of the work). Besides, two premier national research organizations of the country i.e. Indian Council of Medical Research and Department of Biotechnology have set up Task force to understand the causal role of hypovitaminosis-D in the pathogenesis and management of widely prevalent osteoporosis (ICMR) and tuberculosis in Indian population (DBT). The nominee is the coordinator in these projects. He has recently investigated effect of vitamin-D supplementation on muscle strength in women and generated level-A evidence in a study designed randomized controlled trial that was feted with an editorial by the prestigious journal (**J Clin Endocrine Metab 2012, impact factor 6.7**). ***The Journal published an Editorial on this work as a special feature. This work was again carried out in males and lead to similar conclusions (Clin Endocrinol, 2017)**

Ravinder Goswami
Dr R Goswami

(B) Bio-adaptation at molecular level in hypovitaminosis-D in Indians

Vitamin-D and its metabolites act through vitamin-D receptor (VDR) and help absorb dietary calcium in the gut. Dr Goswami has assessed VDR receptor expression in the peripheral blood monocytes and gut (duodenal) mucosa before and after correction of hypovitaminosis-D. The data indicates that Indians are unable to make up for vitamin D-deficiency by over expressing VDR in the gut. This significant observation indicates that in the absence of bio-adaptation at molecular level vitamin-D supplementation is required to normalize serum 25(OH)D levels (**Eur J Clin Nutr 2008, please see updated Bio-data**).

(C) Practical and easy schedule for vitamin-D supplementation in Asian Indians

Professor Goswami has carried out vitamin-D supplementation in vitamin-D deficient subjects and assessed their serum 25(OH)D and PTH response over two months and one year. The supplementation schedule involved one sachet of cholecalciferol (60,000 IU of vitamin-D) given every weeks for 8 weeks and resulted in ideal serum 25(OH)D levels of 32 ng/ml at two months and levels that were double the baseline at one year follow up. This important data establishes the dose of vitamin-D needed by healthy individuals to obtain ideal serum 25(OH)D levels. The work is relevant not only for Indians, but also in global context (**Br J Nutr 2008**). This vitamin-D supplementation schedule devised and validated by Dr Goswami is being used by physicians as standard clinical practice.

(D) Establishing causes for predisposition of Indian women to vitamin-D deficiency related osteomalacia and rickets

The nominee has carried out a family based study involving 98 patients with rickets and osteomalacia and reported that predisposition of females to hypocalcemic osteomalacia is linked not only to the low serum 25(OH)D but also to the low dietary calcium intake. The odds of biochemical osteomalacia in the subjects was reduced by 18% per 15 min daily sunshine exposure and decreased by 10% per 100 mg dietary calcium intake. Vitamin-D receptor and PTH gene SNPs showed no association with osteomalacia/rickets on transmission disequilibrium analysis (**Clin Endocrinol 2008, impact factor 3.4**). His work provided scientific reasons for the predisposition of women to vitamin-D deficiency metabolic bone disorders.

(E) Pathogenesis of sporadic idiopathic hypoparathyroidism

Idiopathic hypoparathyroidism is the second most common cause of chronic hypocalcemia in endocrine practice. The disorder is relatively common in India unlike in the west possibly due to unmasking of their hypocalcemic symptoms in the background of hypovitaminosis-D. The etio-pathogenesis of the illness characterized by hypocalcemia, tetany and cataract was not clear till recently.

The nominee has demonstrated for the first time the role of organ specific autoimmunity (calcium sensing receptor autoantibodies (**J Clin Endocrinol Metab 2013, Impact factor 6.7**), and excluded the role of parathyroid hormone, calcium sensing receptor CTLA-4 (cytotoxic T lymphocyte antigen) and AIRE (autoimmune regulator) gene abnormalities in the pathogenesis of this disorder. (**Eur J Endocrinol 2004, J Clin Endocrinol Metab 2004 & Clin Endocrinol 2006**). Unlike other autoimmune diseases such as type-1 diabetes mellitus and premature ovarian

failure the spread of autoimmunity is limited and does not involve thyroid gland in hypoparathyroidism (**J Clin Endocrinol Metab 2006;91:4256-9 impact factor 5.8**).

Recently Dr Goswami has shown important role of genetic factors in the pathogenesis of isolated hypoparathyroidism by demonstrating a Novel mutation in the GCM2 gene in 10% of the patients. The GCM2 gene encodes for the parathyroid development related transcription factor. This work for the first time shows the important role of genetic factors in the pathogenesis of isolated hypoparathyroidism. The experiments including electrophoretic mobility shift assay and transfection studies showed that R110W change is a loss of function mutation, which could explain loss of parathyroid function at molecular level. Isolated hypoparathyroidism is now be viewed as a heterogeneous group of disorder incorporating a subset who have autoimmune cause and another with genetic cause (**Eur J Endocrinol 2010**).

The latest work of the nominee focused on the pathogenesis of one of important manifestation of idiopathic hypoparathyroidism i.e. Basal ganglia calcification in brain. Though basal ganglia calcification is seen in 70% of the patients, little information was available on its pathogenesis and functional significance. Nominee's extensive work has added novel information on its clinical significance and molecular basis of its occurrence (**Clin Endocrinol 2010, J Clin Endocrinol Metabol 2014**). The nominee investigated the role of 20 important osteogenic molecules including transcription factors related to bone such as 'Runx' and 'Ostrix' and showed that caudate nuclei of the basal ganglia express several osteogenic molecules. The interplay of these molecules could explain the presence of basal ganglia calcification. Thus, basal ganglia calcification can now be viewed as osteogenesis related calcification rather than dystrophic or metastatic calcification. His contribution on pathogenesis of basal ganglia calcification in hypoparathyroidism has been acknowledged by the Editors of J Clin Endocrinol Metab by publishing summary of all of his research work on the Home page of the journal's website in the May 2014 issue. Recently an animal model of the basal ganglia calcification has been developed for the first in the world. This ex-vivo model in using rat striatal cell culture showed the detrimental effect of excessive phosphorus on striatal calcification, which is akin to basal ganglia calcification in humans. Such calcification worsened by calcium and calcitriol therapy in a only in a subset of rats providing basis why the progression of calcification is not observed in all hypoparathyroid patients during prolonged therapy with calcium and vitamin D (Kindly see, **Endocrinology 2020 and J Molecular Endocrinology 2023** in the list of publications.)

(F) Novel clinical features and treatment of the idiopathic hypoparathyroidism

During the last eight years the nominee has studied the world's largest cohort of patients with idiopathic hypoparathyroidism. Besides investigating the etiopathogenesis, the nominee has elicited novel clinical features of hypoparathyroidism such as reversible hypocalcemic neuropathy (**Acta Neurol Scand 2002; 105:128-31**) and spondyloarthropathy (**Clin Endocrinol, 2008; 68:258-63**). The author has demonstrated the important phenomenon of Clinical Remission in patients with isolated hypoparathyroidism, which was so far considered irreversible. This supports the autoimmune basis of the disease (**Clin Endocrinol 2009**, please see list of publication). Dr Goswami has studied the factors associated with presence and progression of basal ganglia calcification and first reported that hyperphosphatemia is the major factor contributing to basal ganglia calcification (**Clin Endocrinol 2012**). Hypoparathyroid patients are usually put on long-

term anticonvulsant therapy to avert hypocalcemic seizures. However, this treatment by itself can lead to several side effects. Recently the nominee has devised a protocol for safely weaning them off this long-term anticonvulsant therapy. This also led to a better calcemic control in these patients (**Eur J Endocrinol 2014**). Recently, nominee has audited the therapy used for the management of hypoparathyroidism patients in India indicating complete efficacy of alfacalcidol in the management (**J Clin Endocrinol Metabol 2019**). Further, through a well conducted RCT, the author also showed equal efficacy of both alfacalcidol and calcitriol in the management of hypoparathyroidism (**J Clin Endocrinol Metabo, 2021**). This is helping physicians in prescribing oral calcium and vitamin D therapy for the management of hypoparathyroidism with confidence rather than tilt for subcutaneous PTH therapy as a routine. As an honor to the nominee contributions in hypoparathyroidism, the nominee has been included as the Indian representative in an international collaborative work on the management of Hypoparathyroidism (Kindly see **Journal of Bone and Mineral Research, 2022**)

The research work of the nominee has provided

(a) New perspectives in the correct diagnosis and treatment of metabolic bone diseases especially vitamin D deficiency, supplementation schedule and basis of food fortification program for urban with indoor life style.

(b) Data regarding organ specific autoimmunity in hypoparathyroidism, which was considered to be idiopathic.

(c) Described new clinical features of hypoparathyroidism, which would help physicians dealing with this disease.

d) Understanding nature of basal ganglia calcification and its determining factors at clinical level and causes at molecular level through in-depth laboratory studies. These studies in brief involved assessment of RNA and protein expression and development of a new ex-vivo animal model i.e. ‘rat striatal cell calcification’ to help understand the unique phenomenon of basal ganglia calcification in hypoparathyroid patients

Summary of the Contribution

Dr. Ravinder Goswami has been a member of the faculty, Department of Endocrinology and Metabolism at AIIMS since 1998. He has made significant original contribution in the field of metabolic bone disorders related to vitamin-D deficiency and idiopathic hypoparathyroidism. The quality of his scientific work has been nationally recognized by the prestigious Shanti Swarup Bhatnagar award (2008), fellowship of the Indian Academy of Science, Bangalore (2007), Indian Science Academy, Allahabad (2011) and National Academy of Medical Science (2013). Dr. R Goswami is a leading investigator in the field of clinical endocrinology of vitamin D deficiency related disorders and hypoparathyroidism. We strongly recommend him for this prestigious medical science award in view of his professional stature and outstanding research contribution which has led to change in management practice of metabolic bone diseases.

Research work on vitamin-D deficiency in India:

Nominee’s work related to vitamin-D deficiency dates since year 2000. He systematically documented for the first that vitamin-D deficiency occurs in apparently healthy Indian subjects especially those working indoors (**Am J Clin Nutr 2000, impact factor 6.1**). This deficiency was related to not only their indoor work conditions but also to the higher melanin content in the skin. His subsequent work demonstrated its causes and significance (**Am J Clin Nutr 2006**), bio-

adaptation at vitamin-D receptor level and associated immune disturbances (**Eur J Clin Nutr 2008 & 2014**). He devised a simple vitamin-D supplementation schedule for Indians to quickly bring these levels to normal for clinical benefit (**Br J Nutr 2008, 2009, Clin Endocrinol 2010**). His work provided scientific reasons for the predisposition of women to vitamin-D deficiency related metabolic bone disorders (**Clin Endocrinol 2008**) and impact of vitamin-D deficiency on thyroid autoimmunity (**Br J Nutr 2009**). He has further investigated effect of vitamin-D supplementation on muscle strength in young females and generated level-A evidence through a randomized controlled trial that was feted with an editorial by the prestigious journal **J Clin Endocrine Metab 2012, impact factor 6.7**). Similar work was also carried out by the nominee in young Indian males (**Clinical Endocrinology 2017**). Nominee's research has triggered several studies from various parts of India as reflected by the citations his papers received. Department of Biotechnology, Govt of India and ICMR have set up Task forces to understand the role of hypovitaminosis-D in various disease. This has led to generation of reference standards for bone mineral density in Indian population published as ICMR Technical Bulletin (April 2011). The data published by the nominee is being used by the National Institute of Nutrition, Hyderabad to formulate guidelines on vitamin-D deficiency in India (<http://icmr.nic.in/final/RDA-2010.pdf>) Page 300-304). Extensive work on vitamin-D deficiency carried out by the nominee is being translated for the benefit of public health and the Government of India has considered strategies for vitamin-D fortification in milk. The information generated by the nominee on vitamin-D deficiency has changed the concepts related to vitamin-D deficiency among physicians in India leading to rational management of metabolic bone disorders. More recently, the author had focused his attention on vitamin D status of economically poor worker mostly outdoors in Delhi. The data generated from a large group constructions worker, hawkers, rikshaw and autorickshaw drivers, gardeners, etc. showed absence of significant vitamin D deficiency in most outdoors. This information is helping physicians in prescribing vitamin D deficiency to only select group of normal Indians affected due to indoor work style and not indiscreetly to all. The information is providing a support to the concept of 'not to use mass and mandatory vitamin D fortification for the whole of Indian population' but only discreetly for indoors (Kindly see, **JBMM, 2017 and Clinical Endocrinology 2019**).

Research work on idiopathic hypoparathyroidism

Hypoparathyroidism is a disorder characterized by tetany, cataract, convulsions and basal ganglia calcification in the brain. Biochemically, it is characterized by hypocalcemia, hypophosphatemia and low serum PTH. The most common form of spontaneous hypoparathyroidism in our country is idiopathic hypoparathyroidism. In order to understand its etiology the nominee has been investigating these patients since 1998 and now has the world's largest cohort of 275 such patients in his follow up for last twenty years. Laboratory studies carried out by the nominee in these patients have helped resolve the pathogenesis of this disorder. He has documented presence of parathyroid autoimmunity and role of mutations in PTH gene and parathyroid development related specific transcription factor *GCM2* in one fourth of such cases. Thus, idiopathic hypoparathyroidism is no longer referred as idiopathic and is now designated as isolated hypoparathyroidism. Nominee's work related to etiopathogenesis of idiopathic hypoparathyroidism has been published in the most reputed Journals of his specialty such as **J Clin Endocrinol Metabol (impact factor 6.7), Eur J Endocrinol (impact factor 4.5) and Clin Endocrinol since 2004**. Nominee has added new information on clinical aspects of hypoparathyroidism such as demonstration of entity called parathyroid spondyloarthropathy, presence of clinical remission in a disorder considered irreversible and effective method to wean them off anticonvulsants. Recently nominee has audited the therapy used for the management of hypoparathyroidism patients and shown that complete efficacy of alfacalcidol in all the Indian patients (**J Clin Endocrinol Metabol 2019**). Further, through a well conducted RCT, the author

also showed equal efficacy of both alfacalcidol and calcitriol in the management of hypoparathyroidism (**J Clin Endocrinol Metabo, 2021**). This is helping physicians in prescribing oral calcium and vitamin D therapy for the management of hypoparathyroidism with confidence rather than tilt for subcutaneous PTH therapy as a routine. As an honor to his contribution in hypoparathyroidism, Dr Goswami has been invited as the Indian representative in an international collaborative work on the management of Hypoparathyroidism (Kindly see **Journal of Bone and Mineral Research, 2022**)

Though basal ganglia calcification is an important clinical feature of hypoparathyroidism, little information was available on its pathogenesis and functional significance. Nominee's extensive work has added novel information on its clinical significance and molecular basis of its occurrence (**Clin Endocrinol 2010, J Clin Endocrinol Metabol 2014**). The basal ganglia calcification is now described as osteogenesis related calcification rather than dystrophic or metastatic calcification. Recently an animal model of the basal ganglia calcification has been developed for the first in the world. This ex-vivo model in using rat striatal cell culture showed the detrimental effect of excessive phosphorus on basal ganglia calcification, which is akin to basal ganglia calcification in humans. Such calcification worsened by calcium and calcitriol therapy in a only in a subset of rats provide the basis so as why the progression of calcification is not observed in all hypoparathyroid patients during prolonged vitamin D and calcium therapy (**Endocrinology 2020 and J Molecular Endocrinology 2023**). Overall, the studies on idiopathic hypoparathyroidism carried out by the nominee have filled gap in the world literature and provided clarity to the physicians on the treatment, pathogenesis and understanding of the disease and its complication, considered idiopathic since 1948.

Translation effect of the nominee's research: The research work carried out by the nominee has changed the clinical practice and triggered research exploring ramifications of vitamin-D deficiency on human health. These operational effects are summarized below

A: National Research coordinating bodies

- **National Institute of Nutrition Hyderabad:** The results of the study carried out by the nominee and published in Am J Clin Nutr 2000, were reproduced in the draft report to support milk fortification with vitamin-D (Source: <http://icmr.nic.in/final/RDA-2010.pdf>) Page 300-304)
- **ICMR** initiated a multicentric task force study in 2002 to look for the prevalence and role of hypovitaminosis-D in osteoporosis with nominee as an investigator. The normative data on bone mineral density of Indians have been generated through this work.
 - **DBT** in 2006 has sanctioned a large study to look for the effect of vitamin-D supplementation on sputum AFB conversion in patients with category-I pulmonary tuberculosis

B: Change in clinical practice

The nominee was the first investigator to report a high prevalence of vitamin-D deficiency in apparently healthy urban Indian subjects (**Am J Clin Nutr 2000**). Demonstration of high prevalence of vitamin-D deficiency and its causes despite living in sunny environment is original information of public health importance. This triggered a large number of studies in India and abroad (citation index of this study-500) and has lead to a shift in management of metabolic bone diseases. Indian physicians are now routinely investigating people with myopathy, backaches and


fractures for the possibility of overt and occult osteomalacia and rickets. The vitamin-D supplementation schedule established by the nominee for overcoming vitamin-D deficiency in Indian population (i.e. 60,000 IU/week for 8-weeks, **Br J Nutr 2008**) is now used as a standard clinical practice. More recently, vitamin D fortification of food has again found its place in common food items in Indian market.

His in-depth work on idiopathic hypoparathyroidism and basal ganglia calcification has helped understand its pathogenesis and provided an autoimmune and genetic basis of this metabolic bone disease. Several of the novel clinical features of this disease as discovered by the nominee are used in the diagnosis and management of hypoparathyroidism all over the world. Absence of calcium sensing receptor mutation in the patients suggested that expensive PTH therapy is not necessary for Indians patients with hypoparathyroidism. Thus, Studies by Dr Goswami in idiopathic hypoparathyroidism and its complication have filled gap in the world literature and provided clarity on the pathogenesis and understanding of the disease considered idiopathic for a long time.

Other work In keeping with the mandate of his department at AIIMS (i.e. investigation of unique endocrine problems in India), the nominee has investigated pathogenesis of hypopituitarism after postpartum hemorrhage, malnutrition modulated diabetes, premature ovarian failure, management of genitourinary infections in diabetes, and adrenal insufficiency in Graves' disease. All these studies are published in high impact journals (such as **Diabetes care, impact factor 7.8** and **JCEM, Impact factor 6.7**) and are summarized in the list of publications.

10. Summary of the most innovative contribution of the nominee (200 words):

The nominee has set an example of Physician-Scientists and work beyond call of duties and given original contribution to the understanding of two important problems. After 12-years of medical education and acquiring highest medical qualification i.e. DM Endocrinology, the nominee has provided services to the patients in the country's busy apex Institute at AIIMS, New Delhi. Realizing the need for quality research in medical field, the nominee worked beyond the call of his duties and has set an example of bed to bench side research. Using his clinical acumen and state of art biomedical research tools, he has contributed in the understanding of hypocalcemic disorders. For his research he was awarded Prestigious Shanti Swaroop Bhatnagar Prize in 2008. Subsequently, he has carried forward his research on the functional significance of Vitamin D deficiency in India through Randomized clinical trials funded by department of biotechnology. His research work on hypoparathyroidism is driven through a largest cohort of patients idiopathic hypoparathyroidism in the world which he has maintained from 1998 till 2023. Briefly, His research work on vitamin-D has helped medical fraternity and community in general in terms of awareness and a supplementation schedule and vitamin D fortification in milk and other foods. His work on idiopathic hypoparathyroidism has clarified several unknown facets of the disease including its appropriate treatment, the pathogenesis of various complication especially basal ganglia calcification including development of a novel ex-vivo animal model. To propagate the culture of much needed physician-scientists among medical fraternity, the nominee as Sub-Dean research at AIIMS initiated a comprehensive hands-on-training program in laboratory-based research. This was aimed to familiarize young medical professionals with state-of-art bench side research to be used in combination with clinical skills.


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