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Review Article

Calciferols: Momentum of these Hormones

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Received: June 29, 2022; **Published:** September 18, 2022

Abstract

The discovery of calciferols is preceded by the recognition of rickets. Herodotus related bone strength to sunlight. Rickets spread in England in the second decade of the 17th century. Glisson described the disease in 1650. In 1918 Mellanby, based on earlier observations, discovered the cause. Concerned about the high incidence of rickets in the UK, following McCollum, he thought that rickets might stem from a dietary deficiency. For his research he examined the diet of the Scots by feeding dogs mainly oatmeal and keeping them out of sunlight. He induced rickets and then cured them with cod liver oil. With these results he thought that vitamin A (discovered by McCollum in 1913) was responsible for the prevention and cure of rickets. In 1922, McCollum found that there was a second fat-soluble factor essential for bone calcification, which he named vitamin D, as the fourth vitamin. The study of calciferols as an "antirachitic factor", a purely nutritional issue, became hormonal thanks to studies on their metabolism (De Lucca); the discovery of its receptors broadened the concept of its actions, among others, the immunomodulators..

Keywords: *Calciferols; Vitamin D; Antirachitic Factor; Vitamin D Receptor; Cod Liver Oil*

Introduction

Calciferols and their receptor agonists - grouped under the vitameric name of vitamin D - are protagonists in the metabolism of calcium and phosphorus, due to their ability to intervene in the intestinal absorption of the mineral calcium. When addressing issues related to vitamin D, it is necessary to refer to bone metabolism, since calciferols are essential both for good skeletal health, as well as for the management of certain bone pathologies and calcium homeostasis.

Three hormones are involved in the metabolism of calcium and phosphorus: parathormone or PTH, vitamin D and calcitonin, as well as growth factors, cytokines and adhesion molecules, necessary for the development and remodeling of bone mass. In the balance of all these factors, the cells that produce calcium-tropic hormones (parathyroid, thyroid and renal parenchyma cells) participate.

The skeletal system is the main destination for the minerals calcium, phosphorus and magnesium, although homeostasis depends on the levels of ionized calcium and phosphate, their absorption and their excretion (renal and digestive) [1]. On sunny days in cities and beaches we are probably more concerned about skin cancer or temporary hot flashes, but we forget that an adequate dose of exposure to the sun is good for our bone health. Write the detailed history of one of the main actors on this stage is thus an excellent contribution to your knowledge.

A book for the bone decade

The work History of vitamin D-authored by the academician Antonio Iglesias-Gamarra and some collaborators- is a monumental review of the subject, from its origins in human history (also of mammals and vertebrates), until the end of the decade of the bone and joints (2000 - 2010) [2]. This first decade of the third millennium was thus consecrated with the support of the World Health Organization (WHO), the Vatican, 44 governments and 750 non-governmental organizations.

The great advance in the knowledge of molecular biology and genetics-in addition to the greater life expectancy of humanity-has highlighted the importance of pathologies of aging, such as osteoporosis, the role of good nutrition in public health, the resurgence of rickets and osteomalacia in vulnerable populations, the genetic and acquired pathologies of the glands that produce calcium-tropic hormones, of the organs that absorb and excrete calcium and phosphorus and of the related receptors [3].

Although this book covers all aspects of the role of calciferols (rickets and osteomalacia, vitamin D-based drugs, controversies on the subject, vitamin D and cancer, physiology and biochemical mechanisms), there is no doubt that his most outstanding contribution is the historical. As a fan of collecting data on different medical histories, I am aware of the substantial work involved in consulting original sources, particularly if this is done comprehensively. I must say that Iglesias - an expert on the subject under review - is an experienced medical historian, as evidenced by his award-winning opera maxima "History of Lupus".

The author is not content with presenting the state of the art of vitamin D, he also wants to know, step by step, how this database was built, what worked or was improved, what was discarded, how this new knowledge influenced human health and as is obvious, who were the thinkers of scientific advance, how things came to them within the relative level of technology and knowledge, and how they were laying the bricks of the building.

For didactic or space reasons, it is common for historical data to be recorded very succinctly, giving the impression that when a discovery was made, the related scientific knowledge would have been clear. This was almost never like that, it took a lot of time and debates; there were even researchers who - having made fundamental observations - did not themselves believe in the soundness of their findings.

If someone wants to read a highly documented review on the subject we are discussing, I suggest the review by Iglesias and his group, with more than 400 references [3]. For this note, I only offer a few [4-17].

The current resurgence of rickets

In developed countries and in regions with long winters with very short days, numerous fortified foods such as dairy products and others-in addition to those naturally rich in calcium and vitamin D such as fish and their oils-guarantee the supply of minimum requirements. However, this does not happen among us, because the sun is often too much, although climatic changes are changing the panorama. Migrant populations are vulnerable to the development of rickets (Figure 1). Also, at risk of being deficient in calciferols are the elderly with little exposure to ultraviolet rays and babies fed breast milk for a long time (deficient in vitamin D) who are also kept confined in closed bedrooms. Likewise, Muslim women who cover their entire body with clothing, such as the chador and other social groups to whom special attention must be paid. Asians with skin characteristics, who have some difference in relation to caucasians and afro-descendants (who, due to their abundant melanin, require excessive ultraviolet rays for the irradiation of their 7-dehydrocholesterol), have plenty of sun in their place of origin, but their diet it is low in vitamin D content, rich in phytic acid from seeds (which store phosphates) and fiber the former gives rise to poorly absorbed calcium phytate salts. In northern countries, infants are breastfed for long periods and almost exclusively, with little exposure to the sun. In both cases, but by different mechanisms, the appearance of rickets is favored.

Figure 1: *Three children with rickets.*

From Sorano to Mellamby

Rickets is perhaps the oldest known vitamin deficiency disease. Dwarfs are observed in Egyptian mummies -some possibly stunted, but it was Sorano (78-117) who referred to this pathology when He stated that learning (to walk) should not be started too early, because the (child's) bones could twist, since they were not yet firm.

Francis Glisson (he of the hepatic capsule), one of the great clinicians of the 17th century, made a complete description of infantile rickets (deformity of the head, thorax and spine) in a book on the subject, in which he affirms that small Patients do not move their joints and tend to lie still. He was struck by the Rickety's thorax, which he compared to the keel of an overturned boat (the center is pointed, and the sides are depressed). When reporting the Sommerset and Dorset epidemic in England, this doctor described the clinic of the disease [4].

For his part, Daniel Whistler (a medical student) in his book Morbo Puerili Anglorum made the first descriptions of rickets, which were possibly used by Glisson. Well-known doctors and researchers in the history of medicine, and others less well-known, made their contributions to this topic. Paré observed cases of spinal and skeletal deviation, Trousseau wrote a paper on rickets and described a sign of latent tetany; furthermore, as Iglesias says in this book, he raised the possibility that rickets was caused by a lack of sun exposure associated with a faulty diet and that cod liver oil could cure it.

Characters of the stature of Virchow, Boerhaave, von Bibra and Marfan among others, also made contributions. According to Ruy Pérez-Tamayo: "The endocrine nature of the parathyroids was demonstrated in 1909 by William G. McCollum and Carl Voetglin, through his studies of renal rickets, a pediatric pathological situation in which children develop bone lesions secondary to kidney failure. These authors observed hypertrophy of the parathyroids and concluded that the reabsorption of calcium from the bones was due to the fact that they regulate calcium metabolism. Their conclusion was reinforced when they managed, through the administration of calcium, to prevent the tetany that occurred after removal of the parathyroids" [4].

In 1915, Collip isolated PTH and demonstrated its action on bone. Erdheim described parathyroid hyperplasia in patients with rickets and osteomalacia. Although the complex relationships between calcium, kidney, bone, parathyroid and vitamin D were beginning to be glimpsed, they were still far from understanding that avitaminosis D or the lack of renal 1-alpha25-$(OH)_2$-vitamin D (which is PTH dependent) caused both the rachitic or osteomalous lesion and the secondary parathyroid hyperplasia, in an effort to maintain normal levels of ionized calcium.

Children in urban areas and temperate climates often developed rickets, which is why this disease was attributed to lack of sun, while others believed it was due to a deficiency of a dietary factor. Until the end of the second decade of the 20th century, Edward Mellanby claimed that both the administration of cod liver oil and exposure to the sun cured rickets.

The vitamins of Eijkman, Funk and Hopkins

The history of vitamins is dense and began with the cure of some diseases with diets that contained certain foods, such was the case of Lind, when he cured the scurvy of English sailors with citrus fruits. Since the end of the 19th century, the cause of beriberi had been studied and it was found that there was a nutritional factor that was not ingested if the basis of the diet was unhusked rice. The discovery (1895) was made by Christian Eijkman when he observed that hens in his laboratory developed polyneuritis (which occurs in beriberi) when mistakenly fed polished rice. By giving them the rice husk, they were cured of the disease. The Dutchman, who was doing these studies on the island of Java, fell ill and had to return to his country of origin [5,7-11,13,14].

After this finding-confirmed by others- several biochemists wanted to fulfill their dream of isolating the antineuritic factor. In 1910, the Pole Casimiro Funk was the one who conceptualized that, if certain substances were lacking in the diet, certain deficiency diseases were produced. This biochemist studied beriberi and found an experimental product that, in very small quantities, prevented the appearance of the disease. Actually, it was an erroneous result, since it was nicotinic acid (which prevents pellagra), but he then proposed the name of vitamins (vital amines) as a generic name for the lacking substances, because he considered them to contain nitrogen, hydrogen and amino radicals, assuming them to be like amino acids. Years later, when vitamin C was found not to be an amine, the term was too popular to change.

In 1912, Frederick Hopkins postulated that some foods contain (in addition to proteins, carbohydrates and fats) "accessory factors". He achieved his results on diets fed to rats, when adding small amounts of milk to their previous diet allowed them to grow. Hopkins had also glimpsed that a diet poor in calcium and phosphorus must produce defective bone calcification. As he did with Banting, after the discovery of insulin, Hopkins turned to research on other matters. Eijkman and Hopkins met in Stockholm in 1929 to receive the Nobel Prize in Medicine for the discovery of the antineuritic vitamin and growth-promoting vitamins, respectively (Figure 2-4).

Figure 2: *Christian Eijkman.*

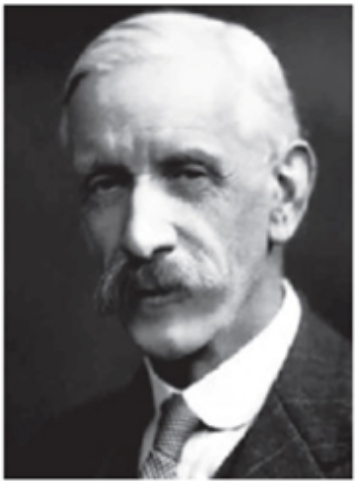

Figure 3: *Frederick Hopkins.*

Figure 4: *Kasmier Funk.*

From antirachitic or fat-soluble factor to hormone D

The careful reading of the book History of vitamin D leads to observe the changes that occurred from the earliest times of evolution to the present and introduces the new concepts that are being implemented in the 20th century. This amid an endemic rickets in North America and Europe, with two world wars that made the researchers true heroes in the midst of those humanitarian disasters [3].

Before modern man, the existence of vitamin D is already foreseen, although *Homo sapiens*, originally from Africa, has black skin to defend itself from the sun, which it receives in abundance. When migrating to Nordic regions, it turns white by adaptation, to be more sensitive to ultraviolet rays and thus defend itself against rickets, a disease that until the 18th century and the Industrial Revolution was rather anecdotal in prevalence.

Rickets (and osteomalacia), beriberi, scurvy, xerophthalmia and pellagra were then identified as public health problems. Food factors began to be investigated and the different vitamins were discovered. Almost imperceptibly, with the advent of new technology and radioactive isotopes, the nutritional version of vitamin D (and deficiency disorders) is becoming the endocrinology of vitamin D, as DeLuca's documented review was titled at the end of the sixties [4].

Iglesias's book goes into so much detail of molecular biology, that it tends to lose the musty smell of historical patina, to become a very complete version of the state of the art, which, although it is also historical, can be accepted only because What is news today is history tomorrow. That is the route of hormone D (1, alpha, 25, dihydroxycholecalciferol), its receptor, agonists, and longevity diseases, such as osteoporosis and renal osteopathy itself.

The Mellanby-McCollum duo and Scott's emulsion

The discovery of fat-soluble vitamins A and D is inevitably linked. Biochemists, nutritionists, pathologists, and paediatricians (alone or in groups) are beginning to scrutinize pathologies such as ocular pathologies in sailors and xerophthalmia in rats fed diets that may point to some nutritional deficiency. It is important to dwell here, on two central characters in the early days of the discovery of vitamins, the Englishman Mellanby and the American Elmer V. McCollum, who would be succeeded by a host of extraordinary researchers, whose findings are noted in detail by the rheumatologist Iglesias.

Let's start with McCollum. He was born on a farm in Kansas, where his natural curiosity allowed him to see calves, pigs, and other animals being born and growing. His father became interested in the study of his children; it was Elmer who, after much "burning the midnight oil," ended up at the University of Wisconsin agricultural school. McCollum was intrigued by the fact that wheat-fed cows did not thrive, went blind and gave birth to stillborn calves; on the other hand, those fed corn did not present health problems [13].

By 1907, biochemistry and nutrition had advanced enough to be able to determine the content of basic nutrients and minerals in foods. In their experiments with wheat and maize, both they contained the same number/amount of macronutrients. What was the difference? Maybe there was something toxic in the wheat? Or maybe it was missing something? McCollum thought it was a better idea to work with small animals instead of cows. He then thought of rats and mice, rodents that ate less, took up less space, reproduced quickly and could be fed controlled diets.

How could a school of agriculture handle rats, such a pest for farmers? the dean questioned. The young investigator ended up working with his small rodents in a basement and secretly. Between 1912 and 1914, McCollum and (Marguerite) Davis treated rats with Hopkins' purified diets (based on pure protein or skim milk, sugar, minerals, or olive oil) and found weight loss that was regained if rodents received butterfat (obtainable from milk, also called butterfat) or egg yolk ten weeks later; however, this did not happen if they received olive oil.

Activity was maintained in the ether soluble fat fraction after saponification of the butter. He called this fat-soluble factor A and that of rice husks (antiberiberi) he called factor B; hence the letters of the vitamins were born. Five months later, Osbourne and Mendel reported that the same beneficial results occurred if cod liver oil was used (Figure 5). Vitamin A (or retinol) had been discovered and was found in the liver of animals and in whole milk, but it was colorless, although it was often associated with beta-carotene (its precursor), which was yellow in color and abundant in carrots, melons and green leafy vegetables.

Figure 5: *Notice of Scott's Emulsion, year 1890.*
The man with the cod in tow became his trademark.

Despite the easy access to vitamins, currently in underdeveloped countries, more than anything else, there are some two hundred and fifty million preschool children with subclinical deficiency and three million with xerophthalmia. Vitamin A deficiency is responsible for 10% of blind children, many of whom die in the first year of suffering from it, as they become especially susceptible to infection and their growth and development are defective.

Shortly thereafter (1918), Mellamby devoted himself to studying rickets by feeding dogs exclusively Scottish oatmeal. She inadvertently kept the pups in dark rooms where they received no sunlight (i.e. no ultraviolet rays) and observed rickets in them. He set out to cure them using various fatty diets, until he achieved a remission of the alterations observed in dogs, particularly with cod liver oil [5,7-11,13,14].

As found in Antonio Iglesias's book, Mellanby considered that "fat soluble factor" (or McCollum's vitamin A) was probably his "anti-rachitic factor A" and recommended cod liver oil as a preventive of rickets. Mellanby and McCollum paid reciprocal attention to their experiments. In 1917, McCollum (already at Johns Hopkins), with the help of the pathologist Park, managed to identify lesions similar to rickets in animals with unbalanced diets in their proportions of calcium and phosphorus, also lacking certain animal fats.

From his early work, in which he isolated vitamin A, McCollum had found that certain foods could contain more than one accessory food substance. To further experiment with Mellanby's finding, he took cod liver oil, heated it, and aerated it to destroy its vitamin A. This treated oil lost its ability to cure twilight blindness but continued to cure rickets! Publishing his findings in 1922, McCollum, following the alphabetical order of vitamins and having already been assigned letters for vitamins B and C, called the new miracle vitamin D. In the meantime, within the Scott and Bowne company in New York, they rubbed their hands: Scott's Emulsion was a preparation rich in natural sources of vitamins A and D! [14].

Then came the rest

In 1923, Goldblatt and Soames identified that when 7-dehydrocholesterol in the skin was exposed to sunlight or ultraviolet rays, an equivalent substance was produced to the fat-soluble vitamin. Hess and Weinstock found that if pieces of irradiated skin were given to rats, rickets could be prevented or cured. Steenbock and Black observed that food irradiated with ultraviolet light acquired the

antirachitic property. In 1933, Koltz used AT-10 (dihydrotachysterol) to treat tetany and in 1934, Collip showed the direct histological effect of parathyroid extracts on bone in nephrectomized animals. In 1942, Patt would show that calcium levels regulate PTH secretion. The German structural biochemist, Adolph Windaus (Figure 6), who later won the Nobel Prize in Chemistry, investigated the structure of vitamins D2 and D3 (ergocalciferol and cholecalciferol, respectively). Of the five vitamins D studied, these last two were the ones that were of practical use [4].

Figure 6: *Adolf Windaus.*

Hormone D In the 1960s, the group led by Héctor F. Deluca [12] (Figure 7) clarified the metabolism of these substances in the body, either through solar irradiation of the skin and the activation of a provitamin D, or by the intestinal absorption of calciferols, these precursors being hydroxylated in the liver and then in the kidney, to give rise to calcitriol, the final hormone with metabolic activity. DeLuca has been an extraordinary researcher in this field, and he is responsible for the recent history of these compounds. These last five decades are those of the exponential growth of the literature on vitamin D, in which pharmaceutical laboratories already appear as important players and where the history, which we are accustomed to reading, becomes a true bibliographic review of a complex problem.

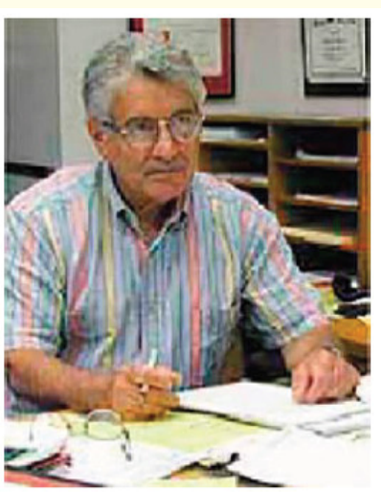

Figure 6: *Adolf Windaus.*

DeLuca himself is the author of around nine hundred indexed articles; he has had famous disciples like Anthony Norman, who is currently doing research at the University of California, Riverside. But since when we think of scientists we think of an underfunded Pasteur or Mellanby himself, it is good to know that this vitamin D expert, in addition to being a professor at the University of Wisconsin and former head of its Department of Biochemistry, has obtained the least eight drugs from his research on calciferols, he owns more than fifteen hundred patents and has hundreds more pending. But his technology has been licensed through the Wisconsin Alumni Research Foundation, bringing millions of dollars in revenue to the university. With the technology developed by him, the company Deltanoid Pharmaceuticals was founded, of which he is president. His department is devoted to the molecular function of vitamins and hormones, and to the metabolism of vitamins A and D.

The importance of vitamins D and their receptor agonists, as impact drugs in the prevention and treatment of diseases of great epidemiological importance such as osteoporosis, is now beyond any doubt. Considering the third part of the book, and a good portion of the second, as a state of the art in the molecular biology of hormone D and its endocrine physiology, I am doing a historical disservice to important modern researchers whom I will not name.

Vitamin, hormone and immunomodulator

Calciferols and vitamin D analogs were initially recognized as antirachitic (nutritional) factors. Subsequently, its hormonal role in mineral and bone metabolism was clarified. More recent studies have investigated aspects such as the photobiology of vitamin D, metabolites, analogs, the CYP enzyme system, the vitamin D receptor, and other additional topics. In particular, the discovery of the receptor and its presence in multiple tissues have led to the "boom" of calciferols, based on their immunomodulatory properties and other mechanisms [12,15-17].

Conclusion

These authors observed hypertrophy of the parathyroids and concluded that the reabsorption of calcium from the bones was due to the fact that they regulate calcium metabolism. Their conclusion was reinforced when they managed, through the administration of calcium, to prevent the tetany that occurred after removal of the parathyroids".

Acknowledgement

The article Calciferols: The momentum of these hormones corresponds to Prologue I written by Dr. Alfredo Jácome-Roca for the book History of vitamin D, edited by doctors Antonio Iglesias Gamarra, José Félix Restrepo Suárez and Carlos Enrique Toro Gutiérrez and published by Simón Bolívar University in 2008. Both the author and the publisher authorized the publication of the article in this journal.

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Volume 6 Issue 2 October 2022