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A list of objectives, requirements, and guidelines are given for a calcium model. Existing models are reviewed and evaluated in relation to the stated objectives and requirements. The reviewed models were either too abstract or apparently invalid. A technical approach to the design of a new desirable model is identified.
PRELIMINARY DESIGN SPECIFICATIONS OF A CALCIUM MODEL

In designing a model of calcium metabolism the primary task is to establish which behaviors of calcium metabolism the model will attempt to simulate. The purpose of the model is to use it as a technique to study altered states of calcium metabolism in bed rest and zero-g. This requires an understanding of short term changes in urinary and fecal calcium and long term changes in urinary, fecal, and bone calcium. It is anticipated that these changes can be explained by altered states of the hormonal regulatory agents of calcium, in particular Vitamin D, parathyroid hormone, and calcitonin at the gastrointestinal tract, kidney, and bone. Other agents such as phosphates, fecal fats, other hormones and electrolytes, piezoelectric forces, and musculoskeletal interactions may also play significant roles. A calcium model capable of describing the behavior of these calcium regulatory agents and the resultant calcium fluxes is the overall objective.

The objectives, requirements, and guidelines for the preliminary design specifications of a calcium model are as follows:

Objectives:

1) to simulate steady-state calcium changes and important interactive biochemical and physiological responses to selected stresses.

2) to simulate the transient responses to the above stresses.

3) to have included into the model, the effects of Vitamin D, parathyroid hormone, and calcitonin on calcium metabolism.

4) To establish plausible mechanistic hypotheses for complex stresses such as spaceflight and bed rest, thereby pointing to areas for investigation regarding calcium homeostasis.

5) Provide a validated baseline model of calcium metabolism which can be improved or updated by the addition of additional mechanisms or improved formulations for various aspects of the model.
Requirements:

1) The important parameters of calcium metabolism to be included in the model will be:
   a) the rate of calcium reabsorbed by the renal tubules, or the rate excreted in the urine.
   b) the rate of calcium absorbed from the gastrointestinal tract.
   c) the rate of calcium secreted into the gastrointestinal tract.
   d) the rate of calcium released or retained by the osteocytic regulation of rapidly exchangeable bone calcium.
   e) the rate of calcium derived from bone resorption by osteoclasts.
   f) the rate of calcium deposited into bone by osteoblasts.
   g) the concentration of plasma parathyroid hormone.
   h) the concentration of plasma 1,25 dihydroxycholecalciferol.
   i) the concentration of plasma calcitonin.

2) The calcium model will be developed as an integrated set of subsystem models, each subsystem describing one particular aspect of calcium metabolism. In this manner, modifications and improvements can be easily made in the model without affecting the other subsystems of the model.

3) The calcium model will be required to simulate responses to the following stresses:
   - Calcium loading or deficiency
   - Phosphate loading or deficiency
   - Vitamin D loading or deficiency
   - Parathyroid hormone loading or deficiency
   - Calcitonin loading or deficiency
   - Changes in dietary calcium or phosphate.

4) Initially only 1-g simulation of the stresses will be required. As the model develops and becomes validated the addition of zero-g simulation will be made. The model will also contain the structure for adding further subsystem simulations, particularly in the area of bone metabolism.
Guidelines:

The purpose of this effort is to find a model that can be used as a tool in understanding the effects of hypogravic environments on bone composition. However, in order to model the mechanisms responsible for changes in bone composition the following facts must be considered.

Bone is a dynamic tissue that appears to have a main function of providing support and structure to the skeletal muscles and body and a minor function of acting as a calcium reservoir in the maintenance of plasma calcium. Bone metabolism may be affected by the physical stresses induced by its primary function or the biochemical alterations induced by either function. The biological effects of the physical stresses, such as piezoelectric effects and tensile or shearing forces are strictly limited to the bone. Bone maintenance is also influenced by calcium metabolism where the kidney and gastrointestinal tract play a significant role. The initial model of this system will not be a bone model per se, but a calcium model encompassing all of the important biochemical calcium regulatory events in the body. Then, as the initial model becomes validated, it can be expanded in the area of bone metabolism. A general description of calcium metabolism is shown in Figure 1.

The initial approach to the development of a calcium model will be to evaluate current existing models and to analyze some of the important aspects of calcium metabolism in terms of the objectives. From this information a technical approach to the design of a calcium model will be identified. The incorporation of a model into the whole-body algorithm will also be evaluated.
Evaluation of Existing Models

Most of the existing mathematical models simulating calcium metabolism are compartmental models. Compartmental models are abstract models designed to reproduce the distribution kinetics of a tracer in a biological system. Because of their power of abstraction, the physiology of the system need not be well understood, but it will not be represented either; therefore, direct interpretation of physiological mechanisms will be limited accordingly.

In 1963 Aubert, Bronner, and Richelle presented a detailed analysis of the many calcium compartmental models and the experimental techniques used to derive those models. For a minimal source of errors, a four compartment pool was required. The arrangement of compartments and the handling of endogenous fecal calcium in terms of gastrointestinal absorption had very little effect upon the absorptions and excretions of calcium; the mass of each compartment and the fluxes between compartments were the main variables affected. However, compartmental variables apparently had little physiological significance. Aubert and Mihaud (1960) hypothesized that the compartments represented serum calcium, extracellular fluid calcium, labile tissue calcium, and less labile tissue calcium, including exchangeable bone calcium. Neer, Berman, Fisher, and Rosenberg (1967), and Massin, Vallee', and Lavoie (1974) were able to demonstrate, however, that the compartments could not be defined in terms of a single body component, nor could a single body component be limited to one compartment.

The objectives of the compartmental models were to describe the fluxes of calcium in normal and stressed man. The data were then related to the physiology of the system and hypotheses were developed to explain the fluxes. The assumptions inherent in the models were 1) the physiological system was compartmentalized and in a steady-state, 2) the amount of calcium in the gastrointestinal tract, therefore, the rate of
absorption was constant, and 3) the calcium balance reflected bone activity; i.e., bone resorption or bone deposition. The models are generally useful in that they demonstrate metabolic calcium responses to selected stresses and have led to the development of hypotheses concerning calcium regulation. Because the compartments and rate constants represent a multitude of physiological processes though, the responsible elements of the control system cannot be resolved.

Long term, or skeletal models were also compartmental models based upon the tracer kinetics and whole-body counting results of strontium. The models of Eisenberg and Gordon (1961), Cohn, et al (1962), and Cohn, et al (1965) are representative of these models. They are based upon the same principles as the calcium models, but include the assumptions that strontium and calcium behave identically in the body and that strontium is retained in skeletal tissues of the body. These models have most of the advantages and disadvantages of the models discussed above except that long term skeletal activity is more clearly defined.

Attempts to define the hormonal regulation of calcium at the bone, gastrointestinal tract, and kidney were made by Aubert and Bronner (1965), Powell (1972), and Powell and Valentinuzzi (1974). Aubert and Bronner (1965) modified a two-compartment model to simulate the regulation of serum calcium by bone metabolism via a feedback loop. The simulations were compared in normal and thyroparathyroidectomized rats. Parathyroid hormone was concluded to change the skeletal control of plasma calcium from a proportional to an integral control. Powell (1972) modified the above model to incorporate the regulatory aspects of plasma calcium upon parathyroid hormone and calcitonin and those in turn upon bone. Powell and Valentinuzzi (1974) made the hormonally induced plasma calcium levels fit Laplace transforms. Unfortunately, the models of Powell (1972) and Powell and Valentinuzzi (1974) do not appear to have been validated. The work is subject to criticism in that rarely biological systems are additive under Laplace transforms because they are often highly nonlinear. This may be particularly true in the case of parathyroid hormone and calcitonin. Additionally, important regulatory features such as the
gastrointestinal tract and the kidney are considered to exert negligible effects. However, current research into calcium metabolism tends to suggest that the kidney is the primary regulator of plasma calcium and that bone is used as a buffer or as a calcium depot or source when the dietary and excretory controls are insufficient. (Nordin, et al, 1975).

Alvi (1969) presented a compartmental analysis of calcium based upon actual physiological compartments rather than abstract compartments. The purpose of the model was to simulate the active and passive fluxes of calcium from one compartment to another in the overall analysis of predictive health monitoring. The physiological compartments were: plasma, red blood cells, interstitial fluid, intracellular fluid, connective tissue fluid, transcellular fluid, and exchangeable bone. Parathyroid hormone and calcitonin were also contained in the model. However, the calcitonin and parathyroid hormones were not sufficiently well defined to satisfy our objectives. Additionally, the accuracy of the simulation is unknown, and the model was not validated by comparison with experimental results.

Technical Approach

The calcium models reviewed fall short of the desired objectives. Extensive research has been done since the discovery of parathyroid hormone, calcitonin, and the metabolites of Vitamin D in deciphering the regulatory features of calcium homeostasis. The influence of diet and hormonal activity at the gastrointestinal tract and kidney and the many feedback mechanisms between the hormones and plasma calcium concentrations are becoming more understood and better defined. The skeleton is perhaps the least understood site of calcium metabolism, but rapid progress is also being made in this area. With the current status of research into calcium metabolism, a calcium model can be developed that will meet all of the stated objectives and requirements.

The calcium regulatory model will be developed as an integrated set of subsystem models. Each subsystem model will simulate one aspect of calcium control. A preliminary estimate of subsystem models may be derived from Figure 1; for example, one subsystem model may describe the activity of 1,25 dihydroxyvitamin D$_3$ upon skeletal calcium, another
describe the resulting plasma calcium concentration upon 1,25 dihydroxy- 
vitamin D₃ metabolism. In this manner, additional mechanisms can be 
added to the calcium model, such as the effects of tensile and compres- 
sional forces upon bone calcium. A subsystem model may also 
be improved without affecting the other subsystems of the model. The 
subsystem models should also be designed within time parameters so that 
the combined models would eventually be capable of performing short, 
intermediate, and long term simulations with the stresses of interest. 
Initially, the control subsystems may be divided into:

a) kidney control 
b) 1,25 dihydroxycholecalciferol control 
c) gastrointestinal absorption control 
d) gastrointestinal secretion control 
e) parathyroid gland control 
f) thyroid gland control 
g) dynamics of rapid exchangeable bone calcium 
h) osteoblastic control 
i) osteoclastic control

As the model progresses and becomes more defined these subsystems will 
probably change.

By dividing the model into subsystems this way, the model perhaps 
may be more easily incorporated into the whole-body algorithm. Important 
sites of interaction may be at the kidney, in terms of glomerular filtration or flow. Further analysis of incorporating the model into the 
whole-body algorithm will proceed the development and validation of the 
calcium model.
Summary

The purpose of this effort was to define a model that is capable of helping an experimenter understand the effects of spaceflight and bed rest on bone composition. Bone composition is influenced by a variety of factors so the approach taken will be directed toward representing systemic regulations of bone metabolism, upon which other factors could be later added. The systemic regulation of bone metabolism can be indirectly determined by calcium metabolism, therefore, available calcium models were examined.

A calcium model that is versatile, flexible, and relatively specific is desired. The model should be capable of testing single, multiple, or sequential stresses, individual or multiple subsystem interactions, and total system hypotheses. It should include a comprehensive set of physiological compartments and control mechanisms and be capable of simulating their dynamic responses to these stresses. It should also be capable of applying the appropriate time frames when necessary under clearly defined subsystem interactions. Modifications of particular parts of the model, or the addition of new parts should be able to be made without disrupting the entire model. The models currently in existence are not capable of meeting the desired objectives. A quantitative model incorporating Vitamin D, parathyroid hormone, calcitonin, and phosphates at the gastrointestinal tract, kidney, and bone is desired. The next stage in the development of the calcium model is a thorough analysis of calcium homeostasis and its endocrine regulation.
REFERENCES


