The Journal of Rheumatology 2023;xx:xxxx
doi:10.3899/jrheum.221150
First Release March 15 2023

The Journal of Rheumatology

Panorama

Inhibition of Local Inflammation by Implanted Gold: A Narrative Review of the History and Use of Gold

Sten Rasmussen, MD, PhD, Professor, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; Chris Frederickson, MSc, PhD, NeuroBioTex Inc, Galveston, Texas, USA; Gorm Danscher, DVM, DMSc, Department of Biomedicine, Aarhus University, Aarhus, Denmark. GD is a partner in Berlock ApS and ReGold ApS. Sten Rasmussen is a partner in ReGold ApS. CF has no conflicts of interest relevant to this article. Address correspondence to Dr. S. Rasmussen, Head of Department, Department of Clinical Medicine, Aalborg University, 249 Selma Lagerløfsvej, 9260 Gistrup, Denmark. Email: sten@dcm.aau.dk.

Gold is highly prized for its luster, is malleable, and may have been among the first metals used for medical purposes by humans. The first documentation of the use of gold metal as a medical device is in 4500-year-old Egyptian mummies. The ancient Egyptians used dental implants in one form or another to replace missing teeth and tried to stabilize teeth that were periodontally involved using ligature wire made of gold.

More than 1700 years ago, Japanese acupuncturists developed and recorded a method known as permanent acupuncture or gold bead acupuncture. The acupuncturist implants the pure gold bead near a painful joint.

Several medical procedures use gold implants for lifetime mechanical purposes because they believe gold will not dissolve, is not biodegradable, is chemically inert, and remains mechanically sustainable. An upper eyelid gold implant in facial neuropathy weighs the eyelid down, allowing easy closure during sleep. For patients who lose their inner ear bones, the ossicles are replaced by prosthetic ossicles made of pure gold. Gold is still in use in teeth for dental repair. Gold marker implantation in the prostate accurately monitors setup errors during external radiation therapy. Therapeutic isotopic nanoparticles show efficacy in treating prostate and lung cancer. Gold is also widely used as a protective coating on stents, pacemakers, or other implanted medical devices to guard and protect the device from biodegradation.

The use of gold-containing soluble drugs in medicine began in the early 19th century. Robert Koch discovered that gold was oligodynamic and that soluble gold complexes can kill tuberculosis bacteria in vitro. He described the use of potassium dicyanoaurate (K [Au $(CN)_2$]) against tuberculosis. The suggestion that the tubercle bacillus was a causative agent for rheumatoid arthritis (RA) led to the use of gold therapy for this disease. Forestier, in 1929, reported on the effect of gold salts on RA, increasing interest in this possibility. In 1941, Freyberg reported the beneficial effect of gold therapy and discovered that small doses were as beneficial as larger doses. Ever since it was found effective against RA in the 1950s, gold compounds have been recommended for several rheumatic and inflammatory diseases. The treatment with gold thio compounds has played a significant role in rheumatology, and clinical trials have shown that gold ions reduce RA inflammation and radiographic progression, and often induce sustained remission. Gold therapy is still in use today and is an effective and inexpensive alternative to more modern biologics or nonsteroidal antiinflammatory drugs, although it must be administered with great care because gold-containing drugs are toxic. Today, gold therapy is replaced by more modern disease-modifying antirheumatic drugs and is investigated for its antibacterial properties.

Metallic gold. The discovery that implanted, solid gold metal converts into soluble gold-containing ionic complexes in the body suggest the gold implant mimics the systemic treatment of gold-containing drugs.[1] In attacking the implanted gold, the macrophages produce clouds of soluble, gold-containing molecules. The gold-containing molecules suppress inflammatory processes and signals. Autometallography[1] visualizes the bio-released gold ions from implanted gold microparticles.

When the gold particles are 20 microns or larger, they are too big for the macrophages to engulf (phagocytose). The macrophages create a dissolution membrane and secrete cyanide ions from the metallic gold surface. Smaller particles, including nanogold, are engulfed by phagocytosis and are transported away from the injection site inside the interior of the macrophage. The gold ions incorporate into the lysosomes inside the macrophages. Gold ions are released within the macrophages and can travel into the interstitial fluid. Nanogold has a short temporal beneficial effect on sterile inflammation. In contrast, the effect of larger gold particles continues to yield relief from pain and inflammation for years after implantation.[2] The reason for this is that gold particles 20 microns or larger stay in place and continue releasing gold ions.

Mode of action of gold at the cellular level. In vitro experiments on activated macrophages show that aurothiomalate inhibits the extracellular release of high mobility group box chromosomal protein 1 (HMGB1) and has no effect on the secretion of tumor necrosis factor.[3] Gold ions cause the inhibition of endogenous mediators of HMGB1 translocation, interferon (IFN)-β, and nitric oxide. HMGB1 provokes the inflammation that might be an underlying cause of the development of RA. HMGB1 is a molecule with dual function and behaves one way inside the nucleus and another outside the cell.

Inside the nucleus, HMGB1 is a player in converting genetic information in DNA to its RNA equivalent. When released from the cell through normal processes or cell death, HMGB1 is a stimulus to the immune system and induces inflammation. Pisetsky[4] emphasizes an unusually high amount of HMGB1 in the synovial tissues and the fluid around arthritic joints. Together with colleagues at the University of Pittsburgh and the Karolinska Institute in Sweden, Pisetsky stimulated mouse and human immune system cells in vitro to secrete HMGB1. They then treated the cultured cells with gold aurothiomalate. They found that the gold ions blocked the release of HMGB1 from the nucleus, reducing the amount available to provoke the body's immune system, thereby reducing the inflammatory response. They suggested that gold inhibits the release of HMGB1 by interfering with the activity of 2 helper molecules that ease the release of HMGB1 from the cell, namely, IFN-β and nitric oxide.[4]

Another biochemical pathway by which gold ions affect tissue and cell biology is through interfering with zinc and zinc-dependent processes. Gold miners use cyanide salts to dissolve gold particles in mining tailings to separate the gold from the rest of the rocks and gravel. To get the dissolved gold back out of the fluid, the miners then add a zinc salt (eg, zinc sulfate), which promptly precipitates the gold as uncharged Au and the cyanide as insoluble neutral $Zn(CN)_2$. In the mine-tailing solutions, the gold cyanide ions react with the zinc to precipitate both metals. In tissue, soluble gold ions displace or interfere with zinc systems. Gold cyanide inactivates the zinc finger transcription factors.[5] The phrase "gold fingers do not work" describes the biochemical effects of gold upon zinc fingers. A somewhat more direct demonstration of the relationship between gold and zinc is the finding of Danscher that the zinc-packed granules of mast cells are depleted of zinc and filled instead with gold after exposure of the cells to a gold solution.[1] Considering how broad the role of zinc is in inflammation, the gold suppression of zinc-dependent processes is likely diverse.

Numerous papers published since 1950 have touted the toxicity of gold in patients who receive gold thio molecules, like aurothiomalate or auranofin, for months to years. The dose of gold in the typical oral or intramuscular administration of the gold-containing compounds for RA is around 100 mg of gold per week. By comparison, micro gold injected into a knee or joint is only 20 mg to 40 mg per joint once in a lifetime,[2] and the release of gold may be in the nanogram range. Because the gold stays in the location injected and is 99.99% pure, toxic effects such as skin rash or organ injury would be implausible.

Gold as a future remedy for rheumatic disease and pain relief. Pain or nociception is a protective sensation in physiological conditions and is of paramount importance to humans and other living organisms, to the extent that it must be considered essential for survival. In some cases, pain becomes part of pathological changes in the brain, and such pathological brain-located pain is often long-lasting, extremely unpleasant, and difficult to treat. Thus, finding an effective treatment that suppresses chronic inflammation and reduces pain is a topic for fundamental researchers and clinical doctors. The safe local gold cure might suppress inflammation and reduce pain, which is the goal of the ongoing research on bioreleased gold ions from gold implants, including gold microparticles.

Experimentally, empirically, and clinically, we know the number of gold ions released from metallic gold implants is sufficient to cause a local effect around the implant.[2] Since gold ions may replace zinc in proteins and may up- and downregulate proteins,[2] there may be an antiinflammatory effect that reduces pain. The inhibition of histamine release from mast cells by monovalent gold ions might also play an antiinflammatory role. Since the findings of macrophage-caused liberation of gold ions in connective tissue,[1] there have been several animal studies pursuing a rational use of gold as a remedy for inflammatory diseases, as well as one clinical trial on human osteoarthritis.[2]

REFERENCES

1. Danscher G. In vivo liberation of gold ions from gold implants. Autometallographic tracing of gold in cells adjacent to metallic gold. Histochem Cell Biol 2002;117:447-52.
2. Rasmussen S, Kjær Petersen K, Kristiansen MK, et al. Gold micro-particles for knee osteoarthritis. Eur J Pain 2022;26:811-24.
3. Zetterström CK, Jiang W, Wähämaa H, et al. Pivotal advance: inhibition of HMGB1 nuclear translocation as a mechanism for the anti-rheumatic effects of gold sodium thiomalate. J Leukoc Biol 2008;83:31-8.
4. Pisetsky DS. Antinuclear antibody testing - misunderstood or misbegotten? Nat Rev Rheumatol 2017;13:495-502.
5. Best SL, Sadler PJ. Gold drugs: mechanism of action and toxicity. Gold Bulletin 1996; 29:87-93.