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Current Treatments For Diabetes Type 2, Osteoporosis, And Hypertension Induced By Glucocorticoids

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Abstract

Glucocorticoids, effective in treating inflammation, can lead to metabolic and skeletal complications, including diabetes type 2, osteoporosis, and hypertension. These complications present significant challenges in clinical management. Unders[1]tanding the underlying mechanisms is crucial for effective management. Lifestyle modifications like dietary changes, weight management, and regular exercise can help mitigate these complications. Pharmacological interventions like antidiabetic medications, bone-strengthening agents, and antihypertensive drugs are often necessary for optimal outcomes. Emerging therapies, such as GLP-1 receptor agonists and SGLT-2 inhibitors, offer promise in addressing these complications. A multifaceted approach involving lifestyle modifications, pharmacological interventions, and emerging therapies is necessary to better meet the needs of patients receiving glucocorticoid therapy and improve their overall quality of life.

Introduction

Glucocorticoids are commonly used to treat autoimmune and inflammatory diseases due to their anti-inflammatory properties. However, prolonged use can lead to adverse effects, including metabolic disturbances and skeletal complications. Prolonged glucocorticoid therapy can induce insulin resistance, impair glucose tolerance, and promote gluconeogenesis, leading to diabetes type 2. Management strategies for glucocorticoid-induced diabetes include lifestyle modifications, pharmacological interventions, and monitoring blood glucose levels. Glucocorticoids can also cause osteoporosis, resulting in decreased bone formation and increased fracture risk. Hypertension, a significant risk factor for cardiovascular disease, can

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be induced by glucocorticoids through mechanisms like sodium retention, potassium excretion, and alterations in the renin-angiotensin-aldosterone system. (**Alan and Alan; 2018**).

Glucocorticoid-Induced Diabetes Type 2

Pathophysiology:

Glucocorticoids are commonly used to treat autoimmune and inflammatory diseases due to their anti-inflammatory and immunosuppressive properties. However, prolonged use can lead to adverse effects, including metabolic disturbances and skeletal complications. Prolonged glucocorticoid therapy can induce insulin resistance, impair glucose tolerance, and promote gluconeogenesis, leading to diabetes type 2. Management strategies for this include lifestyle modifications, pharmacological interventions, and close monitoring of blood glucose levels. Glucocorticoids also affect bone metabolism, leading to decreased bone formation, increased resorption, and impaired calcium absorption, increasing the risk of fractures. Management strategies for this include lifestyle measures, pharmacological interventions, and regular monitoring of bone mineral density. Lastly, glucocorticoids can induce hypertension through mechanisms like sodium retention, potassium excretion, increased vascular tone, and alterations in the renin-angiotensin-aldosterone system. (**Strehl et al., 2019**).

Treatment Strategies

Glucocorticoid-induced diabetes type 2 is managed through a combination of lifestyle modifications and pharmacological interventions. Patients should follow a balanced diet with low glycemic index foods, limiting sugars and carbohydrates. Weight management is crucial for improving insulin sensitivity and glycemic control. Regular physical activity, such as aerobics and strength training, can also improve insulin sensitivity and overall metabolic health. Pharmacological interventions include metformin, which improves insulin sensitivity, reduces hepatic glucose production, and aids in weight management. Sulfonylureas stimulate insulin secretion from pancreatic beta cells and may be used as adjunctive therapy if glycemic control is not achieved with metformin alone. Insulin therapy may be necessary for some patients with suboptimal glycemic control or significant hyperglycemia. Emerging therapies include GLP-1 receptor agonists, which improve glycemic control by increasing insulin secretion, suppressing glucagon secretion, and promoting satiety. SGLT-2 inhibitors work by inhibiting glucose reabsorption in the kidneys, leading to increased urinary glucose excretion and lowering blood glucose levels. (**Guo et al., 2020**).

Glucocorticoid-Induced Osteoporosis

Pathophysiology

Glucocorticoid-induced osteoporosis is a condition that can be managed through a combination of non-pharmacological and pharmacological interventions. Non-pharmacological interventions include calcium and vitamin D supplementation, lifestyle modifications like weight-bearing exercise, and smoking cessation. Pharmacological therapies include bisphosphonates, which inhibit bone resorption by osteoclasts and preserve bone density. Denosumab, a monoclonal antibody, reduces the risk of vertebral and non-vertebral fractures in patients receiving glucocorticoid therapy. Teriparatide, a recombinant form of parathyroid hormone, stimulates bone formation by osteoblasts and is used for severe osteoporosis. Patients receiving glucocorticoid therapy should undergo regular monitoring of bone mineral density

using dual-energy X-ray absorptiometry scans. Regular follow-up visits with healthcare providers are essential to assess treatment efficacy, monitor for adverse effects, and adjust treatment as needed. These strategies aim to prevent and manage glucocorticoid-induced osteoporosis effectively. (**Laurent et al., 2022**).

Glucocorticoid-Induced Hypertension

Pathophysiology

Glucocorticoids can induce hypertension through various mechanisms, including promoting sodium retention and volume expansion in the kidneys, activating the Renin-Angiotensin-Aldosterone System (RAAS), and increasing sympathetic nervous system activity. These changes can lead to increased blood pressure and vasoconstriction. Management of glucocorticoid-induced hypertension typically involves lifestyle modifications and pharmacological interventions. Lifestyle modifications include dietary changes, regular exercise, weight management, smoking cessation, and limiting alcohol consumption. Pharmacological interventions include antihypertensive medications like ACE inhibitors, ARBs, calcium channel blockers, beta-blockers, and diuretics. Regular monitoring of blood pressure and medication adjustments are essential components of hypertension management. Minimizing glucocorticoid dose and duration can help mitigate the risk of hypertension and other adverse effects associated with glucocorticoid use. (**Hunter et al., 2014**).

Treatment Strategies

Pharmacological interventions are often necessary for managing glucocorticoid-induced hypertension, but long-term use can lead to adverse effects. Commonly used antihypertensive medications can cause gastrointestinal problems like nausea, vomiting, diarrhea, and abdominal pain. Long-term use of certain medications, like thiazide diuretics, increases the risk of bone fractures due to alterations in bone metabolism and calcium homeostasis. Each class of antihypertensive medication has its own set of potential side effects, such as dry cough, angioedema, hyperkalemia, renal impairment, peripheral edema, constipation, and electrolyte imbalances. Healthcare providers must weigh the benefits and risks of antihypertensive therapy individually, considering factors like health status, comorbidities, medication tolerability, and potential drug interactions. Regular monitoring and follow-up are essential for assessing treatment efficacy and safety. Lifestyle modifications should be encouraged alongside pharmacological therapy for comprehensive cardiovascular risk reduction. (**Fouad-Elhady et al., 2020**).

Hydroxyapatite

Hydroxyapatite (HAp) is a synthetic bone substitute with chemical similarities to bone matrix, leading to extensive research in biomedical applications. However, its bioabsorbability can vary based on factors such as crystallographic properties and surface characteristics. Smaller grain sizes and higher chemical perfection are generally associated with better bioabsorption, as they allow for easier dissolution and replacement by natural bone tissue. Surface geometry also influences bioabsorption, with a porous or rough surface promoting better integration with bone tissue. The spatial structure of hydroxyapatite crystals affects mechanical properties and biocompatibility, with an optimal spatial structure facilitating cellular attachment, proliferation, and tissue ingrowth. Solubility is another critical factor, with higher solubility allowing for faster dissolution and replacement by new bone tissue. (**Ding et al., 2011**).

Calcium ions are essential for various biological processes and are abundant in many animals. They signal cellular functions like muscle contraction, neurotransmitter release, and gene expression regulation. Calcium is also crucial for bone mineralization, making it abundant in many animals. However, deficiency in calcium can lead to health issues, such as rickets in children and osteoporosis in adults. Calcium deficiency can result in soft and weak bones, especially in postmenopausal women. To maintain optimal health, it is essential to consume adequate amounts of calcium through diet or supplements, including dairy products, leafy green vegetables, fortified foods, and certain fish. Incorporating calcium, vitamin D, and regular exercise can support bone health and reduce the risk of osteoporosis and other calcium-related disorders. (**Mahnam & Raisi, 2017**).

The widespread use of systemic glucocorticoids (GCs) poses significant challenges due to their widespread exposure and adverse effects. These medications affect hundreds of thousands of people, from children to the elderly, and can significantly impact quality of life and healthcare costs. The risks of polypharmacy further underscore the need for interventions to address these issues. A new paradigm has been proposed to address these challenges by developing interventions that target common mechanisms while minimizing side effects. By focusing on shared pathways and GC-related adverse effects, these interventions could improve patient outcomes and reduce the burden of GC therapy.(**Wood et al., 2018)**.

Sweeteners

High-intensity sweeteners (HIS) serve as alternatives to sugar in various food products, beverages, and some oral medications. These sweeteners come in different forms, including natural, semi-synthetic, and synthetic chemical substances. **(Ibrahim; 2015)**

Aspartame

Aspartame is a sweet dipeptide composed of the amino acids aspartic acid and phenylalanine. Its chemical formula is C14H18N2O5, and its full name is N-(L-aspartyl)-L-phenylalanine, 1-methyl ester. Aspartame was discovered in 1965 by James Schlatter. It is approximately 200 times sweeter than sucrose (table sugar) and is commonly used in the food industry to sweeten beverages, preserved foods, candies, and pastries. Once ingested, aspartame is rapidly and completely metabolized in the body into its constituent amino acids, aspartic acid and phenylalanine, as well as methanol. (**Cadirci et al., 2020)**.

The structural features of aspartame, including the negatively charged carboxylic oxygens and the aromatic ring of phenylalanine, have led to the hypothesis that aspartame may enhance or stimulate cation uptake and transport in the body. Aspartame is often chosen as a sugar substitute due to its low-calorie content, which can contribute to reduced calorie intake and potentially lower the risk of various illnesses such as diabetes and cardiovascular diseases. It has been widely used for many decades in diet drinks and food products. Upon oral administration, aspartame undergoes absorption in the gastrointestinal tract, distribution throughout the body, metabolism into its constituent amino acids (aspartic acid, phenylalanine, and methanol), and eventual excretion from the body. (**Mahnam & Raisi, 2017**).

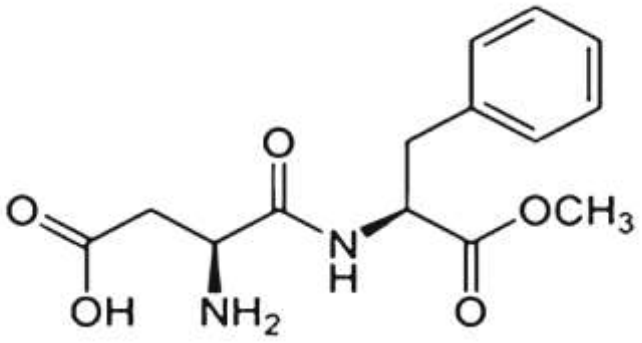

Figure 1: Structure of aspartame (Wikoff et al., 2020)

Aspartame, with its carboxylic acid groups, can bind calcium ions, enhancing calcium absorption in the body. This interaction enhances calcium solubility in the intestine, facilitating calcium transfer into the bloodstream, tissues, and cells. The presence of Asp-Phe in aspartame may reduce the need for excessive calcium intake, preventing imbalances in mineral absorption. This suggests that aspartame's role in calcium absorption could be significant in preventing health issues. (**Hugli & Adams, 2009**).

Aspartame, a drug, has been linked to toxicity concerns due to its potential release of toxic metabolites and potential carcinogenic properties. Despite this, regulatory agencies like the FDA and EFSA have found it safe for normal consumption. Researchers are exploring the development of aspartame nanoparticles to enhance its therapeutic effects while minimizing its toxic side effects. By encapsulating or modifying the structure of aspartame at the nanoscale, researchers aim to improve its safety profile and efficacy. Further research is needed to fully understand the benefits and limitations of these approaches. (**Ashok et al., 2013**)

Aspartame nanoparticles

Nanoparticulate drug delivery systems, including polymeric nanoparticles, liposomes, and nanoemulsions, have revolutionized healthcare and scientific research by improving drug solubility, stability, and bioavailability. These systems enhance pharmacological activity and enable targeted delivery to specific tissues or cells. The effectiveness of nanoparticulate drug delivery systems is largely due to their small size and large surface area-to-volume ratio, which enhance drug dissolution and absorption, leading to more efficient therapeutic outcomes. Additionally, nanoparticulate systems protect drugs from degradation, prolonging their shelf life and ensuring their effectiveness over time. Researchers can customize these systems to meet specific therapeutic needs, enhancing patient outcomes. Overall, nanoparticulate drug delivery systems represent a promising avenue for advancing drug delivery and healthcare outcomes. (**Prakash et al., 2019**)

Polymeric drug delivery systems, based on natural and synthetic polymers, are rapidly emerging in the pharmaceutical industry. These systems enable the introduction of therapeutic substances into the body, improving the rate, time, and place of drug release. Chitosan (CS) biomaterials are versatile and suitable for drug delivery due to their natural, hydrophilic, non-toxic, biocompatible, bio adhesive, and biodegradable properties. CS is obtained through partial N-deacetylation of chitin and consists of D-glucosamine bonded via β(1→4) linkages. **(Islam et al., 2019**).

CS, derived from amino, hydroxyl, and N-acetyl reactive groups, has unique properties that make it applicable in various fields and easily available for interaction with adsorbates. It

is safe, non-toxic, and has become a popular pharmaceutical excipient due to its biocompatibility, biodegradability, low immunogenicity, and cost. CS is hydrophilic and soluble in acidic solutions, but can be degraded by lysozymes, lipases, and proteases. It increases cell membrane permeability, enhancing absorption across intestinal epithelia and opening cell membrane tight junctions. **(Nitta & Numata, 2013**).

Chitosan (CS) is a naturally occurring polysaccharide derived from chitin, found in crustaceans like shrimp and crab. Its cationic properties make it suitable for various medical applications. To enhance its properties, CS can be cross-linked with co-cross-linkers like sulfate, citrate, and tripolyphosphate (TPP), gaining increased stability and encapsulation efficiencies. CS/TPP nanoparticles are ideal for delivering proteins, oligonucleotides, and plasmid DNA due to their submicron size, allowing them to penetrate tissues effectively via blood capillaries. This efficient delivery enhances the delivery of therapeutic agents and ensures their effective distribution within the body. CS/TPP nanoparticles are a promising platform for drug delivery and gene therapy applications due to their high stability, encapsulation efficiencies, and tissue-penetrating capabilities. Their versatility and biocompatibility make them valuable tools in medical research and treatment development. (**Kang et al., 2015**).

The physical crosslinking of polysaccharides like chitosan (CS) uses ionic interactions with ionic cross-linkers like tripolyphosphate (TPP), ensuring reversibility and biocompatibility. This method also provides pH sensitivity, making the nanoparticles suitable for stimuli-sensitive controlled release. This allows for drug release modulation in response to changes in the local environment. By loading bioactive drugs like aspartame into CS/TPP nanoparticles, the unique properties of the nanoparticulate drug delivery system can be leveraged to enhance the biodegradable polymers, potentially leading to the development of effective treatments for conditions like osteoporosis. This approach offers potential benefits such as improved drug stability, enhanced bioavailability, and controlled release kinetics.(**Nitta & Numata, 2013**).

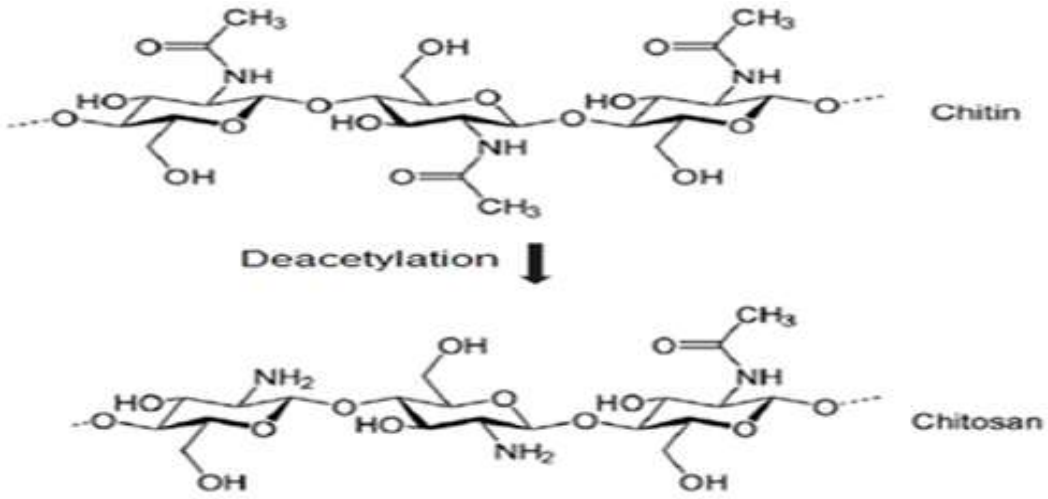

Figure 2: The structure of chitin and chitosan (Wahba, 2020)

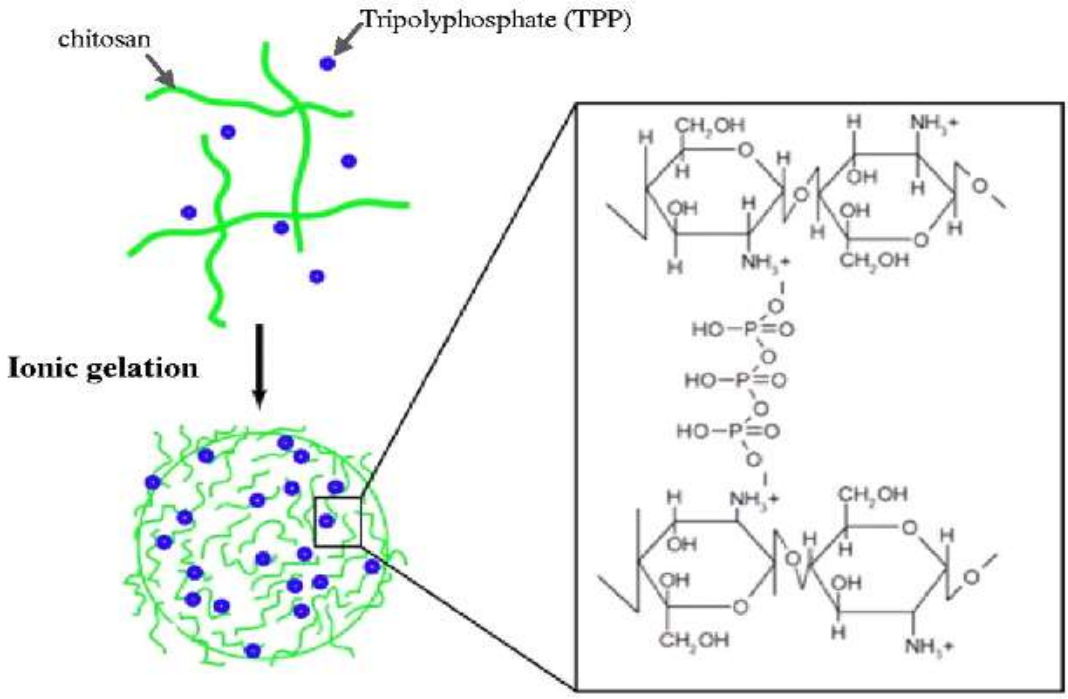

Figure 3: Ionotropic gelation creates a chitosan-tripolyphosphate complex, as shown in a schematic example. (Chavez de Paz et al., 2011).

Conclusion

Glucocorticoid-induced diabetes type 2, osteoporosis, and hypertension are significant health issues for patients undergoing long-term glucocorticoid therapy. To manage these complications, a comprehensive approach includes lifestyle modifications, pharmacological interventions, and emerging therapies. Lifestyle changes, such as dietary changes, weight management, regular physical activity, and smoking cessation, can mitigate the adverse effects of glucocorticoid therapy and improve overall health outcomes. Pharmacological interventions, such as metformin, bisphosphonates, and ACE inhibitors, are often necessary to achieve glycemic control, preserve bone density, and lower blood pressure. Emerging therapies like GLP-1 receptor agonists and SGLT-2 inhibitors show promise in addressing these complications. Further research is needed to identify novel therapeutic targets and optimize treatment strategies, ultimately improving outcomes and quality of life for patients undergoing glucocorticoid therapy.

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