CORTI SUPPORT

Calcium loss and other imbalances in patients chronically treated with systemic glucocorticoids (GCs)

Scientific overview

Companion Therapeutics

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1. DESCRIPTION AND USE

CORTI Support is a dietary supplement specifically designed to maintain healthy levels of minerals and amino acids, which may be significantly reduced in patients treated with long-term oral glucocorticoids such as: Budesonide, dexamethasone, methylprednisolone, prednisolone or triamcinolone, among others.

2. PHARMACOLOGICAL BACKGROUND

Glucocorticoids (GCs) are steroids that reduce inflammation throughout the body. Cortisol is a naturally occurring GC that is synthetized by the adrenal glands, and works to regulate inflammation and other processes in the body.

Synthetic GCs are drugs including those listed in table 1, which act in a similar way to stop inflammation, and can be even more potent than naturally occurring chemicals.

A	F	P
Alclometasone	Fludroxycortide	Paramethasone
B	Flumetasone	Perdesonide
Beclometasone dipropionate	Flunisolide	Prednisolone
Betamethasone dipropionate	Fluocinonide	Prednisone
Budesonide	Fluocortolone	Prednylidene
C	Fluorometholone	Pregnadiene
Chlormadinone acetate	Fluticasone	Pregnatriene
Chloroprednisone	**H**	Pregnene
Ciclesonide	Hydrocortamate	Proctosedyl
Cortisol	17-Hydroxyprogesterone	Progesterone
Cortivazol	**M**	Promestriene
Cortodoxone	Medroxyprogesterone acetate	**R**
Cyproterone	Megestrol acetate	Rimexolone
D	Meprednisone	**T**
Deflazacort	Methylprednisolone	Tetrahydrocorticosterone
Delmadinone acetate	Mometasone furoate	Tetrahydrogestrinone
Dexamethasone	**N**	Tixocortol
5α-Dihydrocorticosterone	Nestorone	Triamcinolone
		U
		Ulobetasol

Table 1. Synthetic GCs

Pharmacologic doses of GCs are used to treat patients with inflammatory, allergic and immunological disorders. The most common disorders in which the GCs are particularly useful are listed below:

Autoimmune diseases	Allergies
Multiple sclerosis	Allergies
Rheumatoid arthritis	Asthma
Inflammatory bowel disease	**Cancer**
Ulcerative colitis	Lymphoblastic leukemia
Psoriasis	Hodgkin's lymphoma
Eczema	Non-Hodgkin's lymphoma
Crohn's disease	Multiple myeloma
Adrenal insufficiency	**Surgery**
Addison's disease	Neurosurgeries to reduce inflammation in delicate tissues
Surgical removal of adrenal glands	Organ transplant to help prevent early rejection

Table 2. Disorders in which GCs are commonly used

During the chronic therapy with oral GCs, the supraphysiologic exposure has many adverse effects, ranging from suppression of the hypothalamic-pituitary-adrenal axis and Cushing's syndrome to infections and changes in mental status.

Prolonged high-dose GCs therapy has many potential side effects. Side effects resulting from GCs use are common and potentially serious, including those related to the musculoskeletal, endocrine, gastrointestinal, immune, cardiovascular and central nervous systems.

2.1. Musculoskeletal adverse effects

Bone loss is one of the most common and debilitating side effects associated with prolonged high-dose GCs therapy. Bone loss associated with GCs therapy is most pronounced in the first few months after initiating treatment.

GCs use can also cause myopathy. The onset of symptoms is usually subacute and over several weeks or months. Higher doses of GCs are associated with earlier onset of symptoms. (Moghadam-Kia & Werth, 2010)

GCs are a common cause of avascular necrosis, particularly in the femoral head. The overall incidence of GCs-induced avascular necrosis is low. The mechanism by which GCs produce avascular necrosis is not fully understood.

Since the incidence of avascular necrosis is low, and the mechanism by which this adverse effect is produced is still unknown, this potential side effect is not part of the scope of CORTI Support.

2.2. Endocrine adverse effects

GCs decrease glucose utilization and increase hepatic glucose production, leading to hyperglycemia.

The influence of GCs in serum lipid levels is still controversial. Although there is a study which suggest that GCs produce an elevation in TG, TC and LDL, in addition to decreased levels of HDL, other prospective studies have suggested that GCs may not have an adverse effect on serum lipids.

In one study, for example, prednisone therapy (20 mg/day tapered to 5 mg/day during three months) had no significant adverse effect on serum lipids after adjustment for other risk factors. (Svenson, Lithell, Hällgren, & Vessby, 1987) Another study examining the relationship between GCs use and lipid profile, using the data from 15.004 participants in the Third National Health and Nutrition Examination Survey, suggests that GCs therapy may be associated with a favorable lipid profile in patients ages 60 years and older. (Choi & Seeger, 2005)

Since the influence of the GCs, in serum lipid levels is still controversial, this potential side effect is not part of the scope of CORTI Support.

2.3. Gastrointestinal adverse effects

The use of systemic GCs is associated with gastrointestinal side effects including gastritis, peptic ulceration, and gastrointestinal hemorrhage. Although GCs have been shown to increase the risk of peptic ulceration and GI bleeding, the shown effect could be in part due to concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs).

Since the influence of the GCs, in gastrointestinal side effects could be related to concomitant use of NSAIDs, this potential side effect is not part of the scope of CORTI Support.

2.4. Immunological adverse effects

The use of GCs is associated to infections; however, this side effect is due to the inhibition of the immune system caused by the GCs, which is precisely their mechanism of action. Since GCs are commonly used in autoimmune diseases, and the boost of the immunological system is contraindicated in patients with autoimmune diseases, CORTI Support does not contain any component aimed to increase the immune response in order to avoid possible infections.

2.5. Central nervous system and cardiovascular adverse effects

These two groups of side effects are not in the same level of severity compared to musculoskeletal and endocrine side effects. On the other hand, these kinds of adverse effects can be hardly impacted by a dietary supplement. Accordingly, these two group of side effects are not included in the scope of CORTI Support.

3. NUTRITIONAL DEFICIENCY MECHANISM

According to the rationale in the chapter number two, the most relevant adverse effects associated with the use of GCs are: Bone loss, myopathy and increased serum levels of glucose. These three adverse effects have a common factor, all of them are produce through a nutritional deficiency.

The mechanisms through which these nutritional deficiencies – side effects are produced, are summarized below.

3.1. Calcium loss and bone loss

GCs alter calcium homeostasis reducing bone formation and increasing bone resorption, which finally leads to loss of bone mass. (Adler & Rosen, 1994) (Lane & Lukert, 1998)

3.2. Protein catabolism and myopathy

GCs use can cause myopathy by direct catabolic effect on skeletal muscle via activation of the glucocorticoid receptor. (Moghadam-Kia & Werth, 2010) The reduction of potassium and phosphate serum levels are also related to GCs induced myopathy. (Chawla, 2011) (Gupta & Gupta, 2013)

3.3. Chromium loss and increased serum levels of glucose

GCs administration leads to insulin resistance in experimental animals and humans. Steroid-induced diabetes is more prominent in subjects who have impaired glucose tolerance or diabetes prior to the GCs treatment. However, GCs have been shown to induce glucose intolerance even in control subjects.

The mechanisms responsible for steroid-induced diabetes are unknown but decreased insulin sensitivity is an overlying cause.

Steroid-induced diabetes was associated with increased chromium losses. On the other hand, insufficient dietary chromium is associated with glucose intolerance and diabetes, so the depletion in chromium levels, produced by GCs, seems to be associated to steroid-induced glucose intolerance. (Ravina, et al., 1999)

4. RELATED ADVERSE EFFECTS

As mentioned in the chapter number two, the adverse effects associated with chronic use of oral GCs can be classified in 6 groups, as shown in table 3.

Musculoskeletal	Gastrointestinal
Osteoporosis	Gastritis
Myopathy	Peptic ulceration
Avascular necrosis	Gastrointestinal hemorrhage
Cardiovascular	**Endocrine and metabolic**
Hypertension	Serum lipids increase
Obesity	Serum glucose increase
Immune system	**Central nervous system**
Infections	Behavioral and cognitive changes

Table 3. Ptential adverse effects to GCs

However, according to the reasons that were widely explained in the chapter number two, this product is focused in the three main adverse effects, namely bone loss, myopathy and serum glucose increase.

4.1. Bone loss

Bone loss is one of the most common and debilitating side effects associated with prolonged high-dose GCs therapy. Bone loss associated with GCs therapy is most pronounced in the first few months after initiating treatment. (Moghadam-Kia & Werth, 2010)

4.2. Myopathy

Subjects with glucocorticoid induced myopathy typically present with proximal muscle weakness and atrophy in both the upper and lower extremities. (Moghadam-Kia & Werth, 2010)

4.3. Increased serum levels of glucose

In a case-control study quantifying the risk of developing hyperglycemia requiring hypoglycemic therapy after oral GCs use, the estimated relative risk in patients taking GCs was 2.23 (95% CI, 1.92 to 2.59) in comparison with nonusers. The risk increased proportionally with increasing GCs dose.

5. FORMULA

SUPPLEMENT	AMOUNT PER SERVING	% DAILY VALUE	RATIONALE
Vitamin D3 (as cholecalciferol)	800 IU	200 %	Calcium loss and bone loss (Guarantees calcium absorption)
Vitamin K2 (as Menaquinone-7)	100 µg	125 %	Calcium loss and bone loss (Guarantees calcium fixation)
Calcium (as calcium carbonate)	1.000 mg	100 %	Calcium loss and bone loss
Chromium (as chromium picolinate)	200 µg	167 %	Chromium loss and increased serum levels of glucose
Potassium (as dipotassium phosphate)	89,8 mg	3 %	Bone loss
Proprietary blend	850 mg	*	
L-glutamine			Muscle catabolism
L-isoleucine			Muscle catabolism
L-leucine			Muscle catabolism / Glucose levels
L-valine			Muscle catabolism

***Daily value not established**

Serving size: 4 capsules
Servings per container: 30 servings or 120 capsules

6. FARMACEUTICAL DOSAGE FORM PACKAGING MATERIAL

"00" standard two-piece hard gelatin purple/purple capsule, where each capsule contains 625 mg of calcium carbonate, equivalent to 250 mg of calcium + 5 µg of cholecalciferol, equivalent to 200 IU of vitamin D3 + 25 µg of menaquinone-7 + 50 mg of dipotassium phosphate + 1,6 mg of chromium picolinate, equivalent to 200 µg of chromium + 212,5 mg of a proprietary blend containing L-glutamine + L-isoleucine, + L-leucine + L-valine.

120 capsules bottled in a 250 CC white HDPE bottle / 45mm white ribbed CRC cap with heat seal /4 color process label /cotton / desiccant.

7. RATIONALE OF THE COMPONENTS

7.1. Calcium carbonate and vitamin D3

The American College of Rheumatology Ad Hoc Committee on Osteoporosis suggests that individuals receiving GCs maintain a calcium intake of 1.000 to 1.500 mg/day and vitamin D intake

of 800 IU/day through either diet or supplements. (Glucocorticoid-Induced, 2001) (Grossman, et al., 2010)

The recommendation issued by the American College of Rheumatology is based on the revision of all the available scientific literature, which clearly shows the benefit of supplementing calcium and vitamin D in patients receiving high doses of GCs. The evidence is huge (Sambrook, et al., 1993) (Buckley, Leib, Cartularo, Vacek, & Cooper, 1995) and the college classifies this evidence as level A, which means: Multiple population evaluated and data derived from multiple randomized clinical trials or meta-analysis.

The most commonly used calcium salt in dietary supplements in the USA is carbonate. Of 6135 dietary supplements containing calcium, 1729 (28%) use carbonate as the salt. The second most commonly used salt is citrate with 1261 (20.6%) products. On the other hand, most of the clinical trials in which the efficacy of calcium supplementation is shown, were performed using calcium carbonate. According to that, calcium carbonate was the selected calcium salt for CORTI Support.

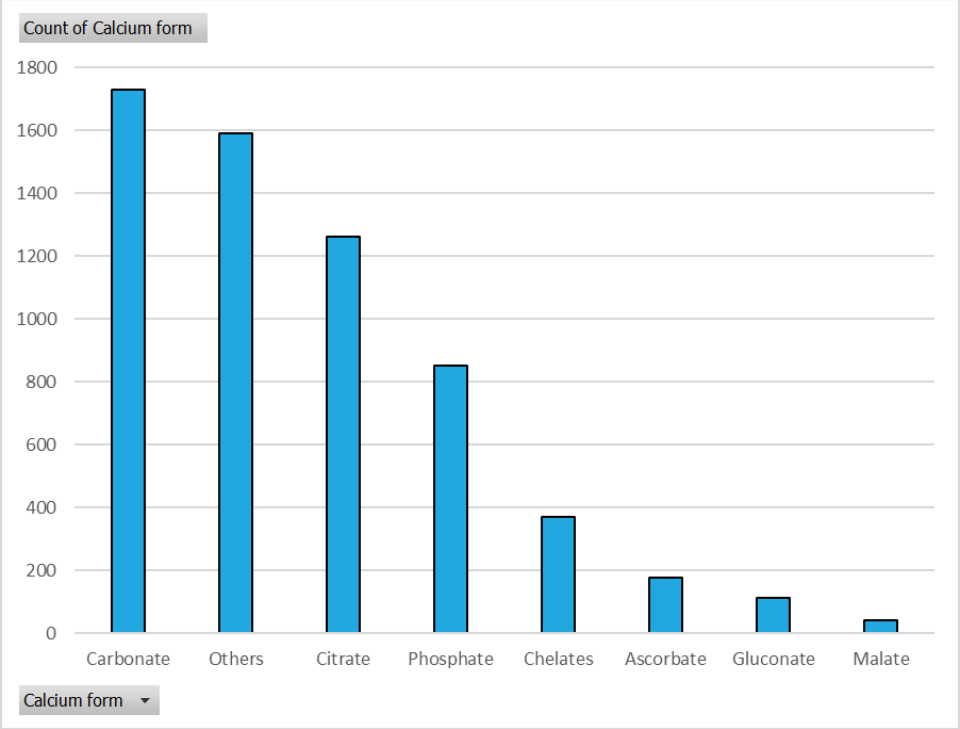

Figure 1. Most used calcium salts in dietary supplements in the U.S. (unidose dosage forms)

The amounts per serving of 1000 mg for calcium and 800 IU for vitamin D3 were selected according to the recommendations of the American College of Rheumatology. The product was designed to be administered twice daily. The amounts per serving of 1000 mg for calcium and 800 IU for vitamin D3 in CORTI Support were compared to the amounts in the total population of dietary supplements in the U.S. The comparison was performed by using the Dietary Supplement Label Database of the

National Institute of Health, and the findings showed that the content of calcium and vitamin D3 in CORTI Support are above the median. (See figures 2 and 3) (NIH Office of Dietary Supplements, 2015)

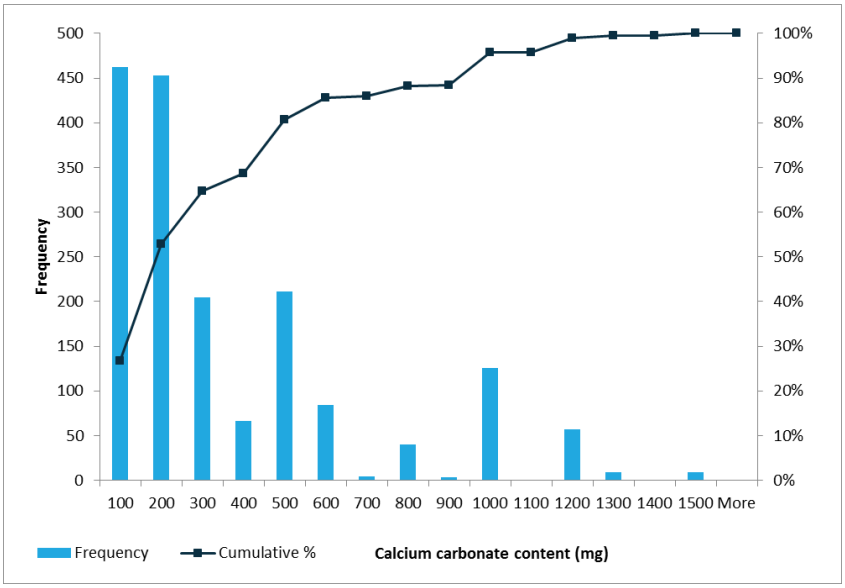

Figure 2. Calcium (as calcium carbonate) content in dietary supplements in the U.S. (unidose dosage forms)

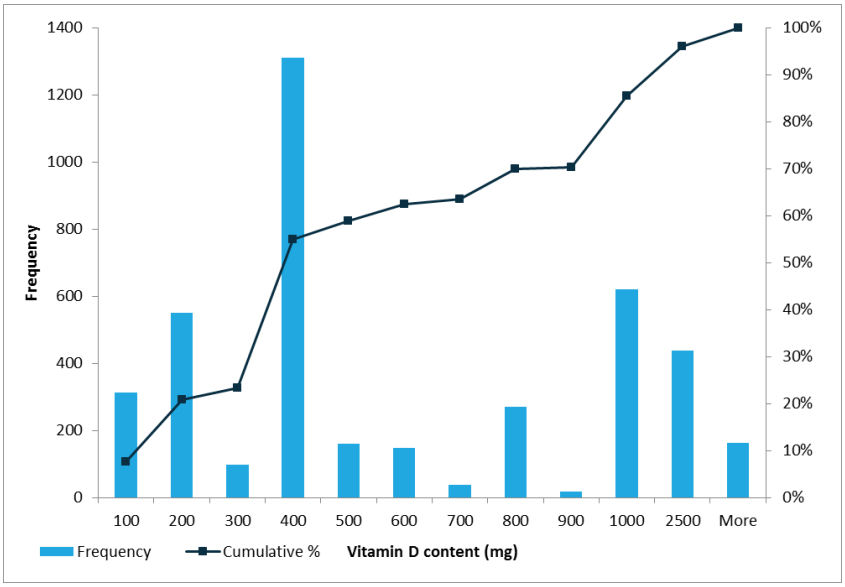

Figure 3. Vitamin D content in dietary supplements in the U.S. (unidose dosage forms)

7.2. Vitamin K2 (Menaquinone-7)

Recently, vitamin K2 has shown to work synergistically with a number of other nutrients, including calcium and vitamin D.

Vitamin K is actually a group of fat-soluble vitamins. Of the two main ones, K1 and K2, the one receiving the most attention is K1, which is very easy to get through the diet. Vitamin K2, also called menaquinone, is made by the bacteria that line the gastrointestinal tract; K2 goes straight to the blood vessel walls, bones, and tissues other than the liver.

Vitamin K2 can be broken into two additional categories, called MK-4 (menaquinone-4) and MK-7 (menaquinone-7). MK-7 is a longer-chain forms found in fermented foods. There's a variety of these long-chain forms but the most common one is MK-7. This is the one which is desirable to find in food supplements, because in a supplement form, the MK-4 products are actually synthetic. They are not derived from natural food products containing MK-4.

The MK-7 (long-chain, natural bacterial-derived vitamin K2) is obtained from a fermentation process, which offers a number of health advantages; it stays in the body longer, and It has a longer half-life, which means you can just take it once a day in very convenient dosing.

When you take vitamin D, the body creates more vitamin K2-dependent proteins, the proteins that will move the calcium around. They have a lot of potential health benefits. But until the K2 comes in to activate those proteins, those benefits aren't realized. So, if you're taking vitamin D, the body creates an increased demand for K2. Vitamin D and K2 work together to strengthen the bones.

Several studies have shown the relationship between calcium, vitamin D and vitamin K2. (Zittermann, 2001) (Flore, et al., 2013) (Gajic-Veljanoski, Bayoumi, Tomlinson, Khan, & Cheung, 2012) (Huang, et al., 2015)

Most of the studies were performed by using 100 µg of vitamin K2 per day. According to that, the amount per serving of vitamin K2 in CORTI Support is 100 µg.

The amount per serving of 100 µg for vitamin K2 in CORTI Support was compared to the amounts in the total population of dietary supplements in the U.S. The findings showed that the content of vitamin K2 in CORTI Support is above the median. (See figure 4) (NIH Office of Dietary Supplements, 2015)

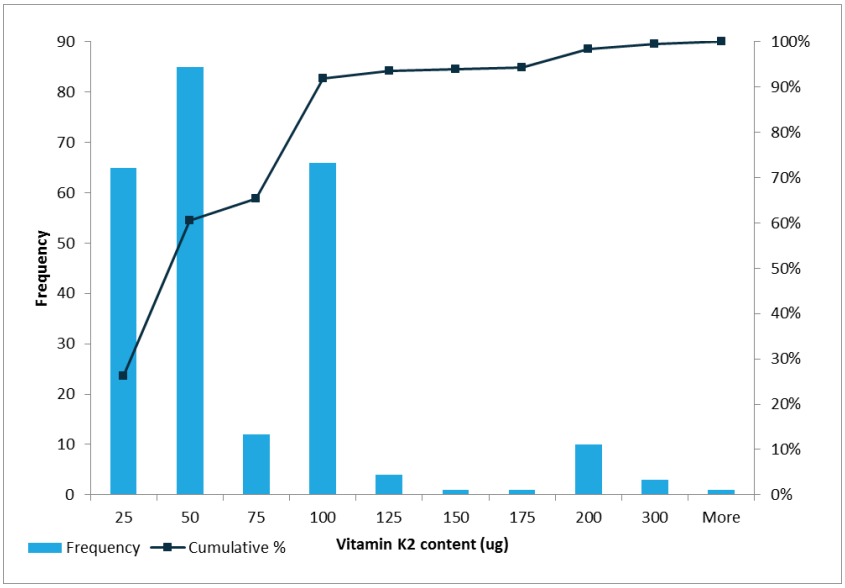

Figure 4. Vitamin K2 content in dietary supplements in the U.S. (unidose dosage forms)

7.3. Potassium phosphate

One of the mechanisms by which the GCs produce myopathy is the reductions of the serum levels of potassium, (Chawla, 2011) (Gupta & Gupta, 2013) so potassium supplements have been used in order to prevent this adverse effect. (Chawla, 2011)

Phosphate serum levels have also been reported as affected in the GCs induced myopathy.

Potassium phosphate is an easy way to supplement both, potassium and phosphate at the same time. Most of the products containing potassium phosphate in the US, contain 200 mg. According to that, the amount per serving of potassium phosphate in CORTI Support is 200 mg.

7.4. L-glutamine

L-alanyl-L-glutamin and L-Glutamine have also been used as a treatment for GC's induced myopathy. (Rodrigues Pereira & Freire de Carvalho, 2011) (Gupta & Gupta, 2013) (Hickson, Wegrzyn, Osborne, & Karl, 1996) (Schakman, Gilson, & Thissen, 2008) (Salehian, Mahabadi, Bilas, Taylor, & Ma, 2006)

The amount per serving of 250 mg for glutamine in CORTI Support was compared to the amounts in the total population of dietary supplements in the U.S. The findings showed that the content of glutamine in CORTI Support is above the median. (See figure 5) (NIH Office of Dietary Supplements, 2015)

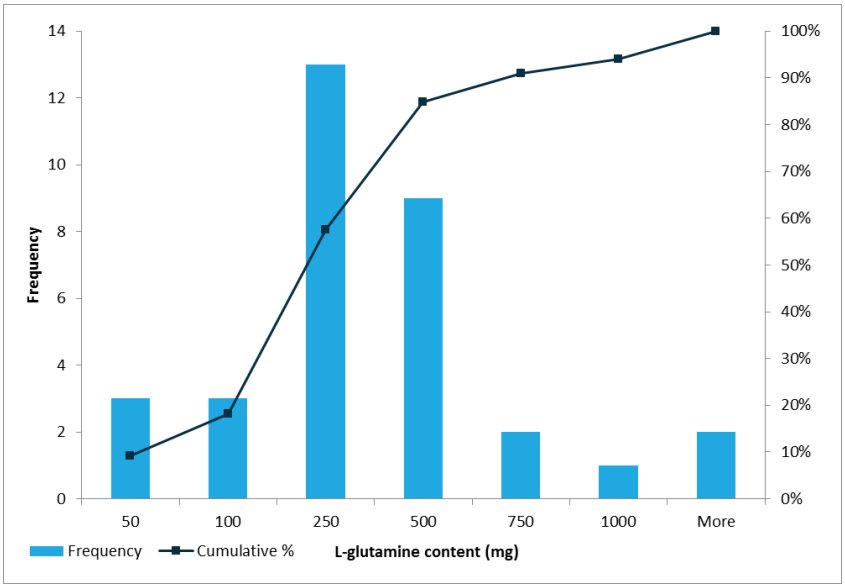

Figure 5. L-glutamine content in dietary supplements in the U.S. (unidose dosage forms)

7.5. L-Isoleucine

Isoleucine has clearly shown its hypoglycemic effect in several preclinical trials. (Doi, Yamaoka, Nakayama, Sugahara, & Yoshizawa, 2007)

The schematic diagram in figure 6 shows the effect of isoleucine on glucose metabolism.

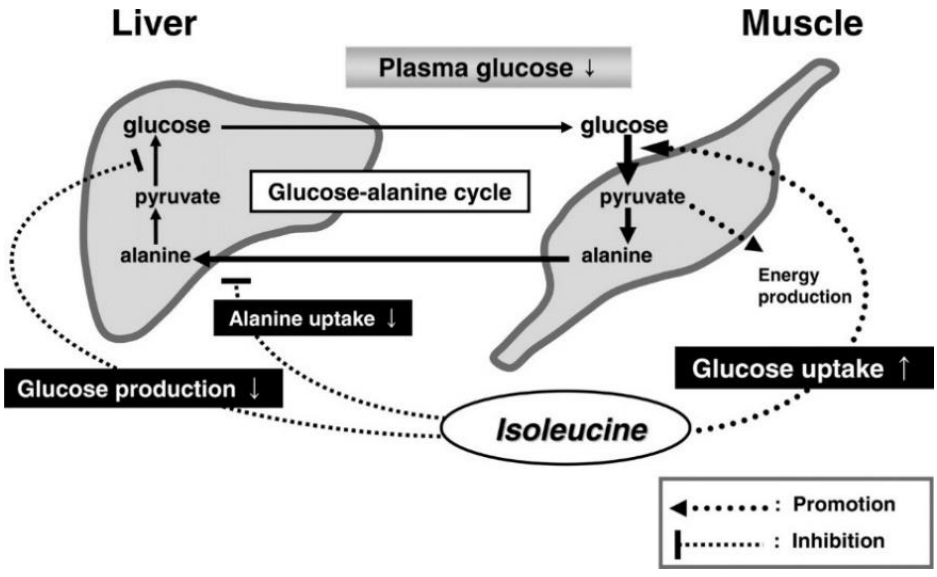

Figure 6. Schematic diagram of the effect of Ile on glucose

Isoleucine, a potent hypoglycemic amino acid, stimulates glucose uptake in skeletal muscle, and the incorporated glucose is oxidized without significant elevation of the plasma insulin level. In liver, isoleucine decreased the hepatic gluconeogenic enzyme activity and glucose production. These mechanisms are responsible for the hypoglycemic effect of isoleucine that improves the energy state of the muscle and liver and that may improve insulin resistance in vivo. (Doi, Yamaoka, Nakayama, Sugahara, & Yoshizawa, 2007)

On the other hand, isoleucine, as a branched chain amino acid, participate in the synthesis of muscle proteins, giving to this component a double role into the formula of CORTI Support.

The amount per serving of 250 mg for isoleucine in CORTI Support was compared to the amounts in the total population of dietary supplements in the U.S. The findings showed that the content of isoleucine in CORTI Support is above the median. (See figure 7) (NIH Office of Dietary Supplements, 2015)

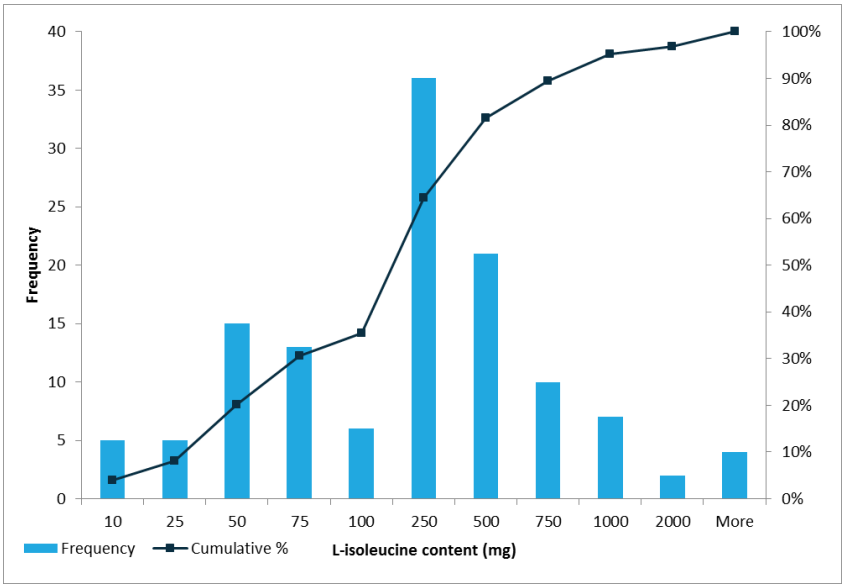

Figure 7. L-isoleucine content in dietary supplements in the U.S. (unidose dosage forms)

7.6. Chromium picolinate

Chromium is an essential nutrient involved in the metabolism of glucose, insulin and blood lipids. Suboptimal dietary intake of chromium is associated with increased risk factors of diabetes and cardiovascular diseases. Severe neuropathy and glucose intolerance of patients on total parenteral nutrition, who was receiving currently recommended levels of chromium, were reversed by additional supplemental chromium. Chromium increase insulin binding to cells, insulin receptor number and activates insulin receptor kinase leading to increased insulin sensitivity. (Anderson, 2000)

Since the essential nutrient chromium improves insulin sensitivity, and stresses that alter blood glucose levels often lead to increased Cr losses, it was postulated that chromium may be involved in the prevention and regulation of steroid-induced diabetes. GCs administration was also shown to increase Cr losses. (Anderson, 2000)

Supplementation of three patients with steroid-induced diabetes led to a reversal of the signs and symptoms of diabetes. To confirm these results, 50 patients with uncontrolled steroid-induced diabetes were supplemented with Cr. Patients all had fasting blood glucose values greater than 13.9 mmol/L that did not respond satisfactorily to hypoglycemic drugs and/or insulin therapy. The duration of the corticosteroid treatment varied depending upon the nature of the illness. The steroid-induced diabetes of 47 of the 50 patients was controlled by supplemental Cr, 200 µg of Cr as Chromium picolinate, 3 times daily. (Ravina, et al., 1999)

Prior to the initiation of supplemental Cr, hypoglycemic agents were also reduced 50 %. Following two weeks of 600 µg per day of supplemental Cr, daily Cr intake was reduced to 200 µg. Five patients were able to stop all forms of hypoglycemic medications and blood glucose remained normal simply by taking 200 µg of Cr daily. Three patients stopped taking chromium as well as their medications. However, blood glucose started to increase but returned to acceptable levels upon the restoration of supplemental Cr, 200 µg per day. Patients continued to receive GCs treatment. (Ravina, et al., 1999)

Although GCs therapy carries a risk of promoting or exacerbating hyperglycemia, there are currently no established medical guidelines for detecting or managing patients initiating GCs therapy. While improved Cr nutrition may be of benefit to a significant portion of the general population, it may be of particular importance to those who are treated with corticosteroids. (Ravina, et al., 1999)

According to the available clinical trials, (Ravina, et al., 1999) the maintenance dose of chromium, in order to keep the blood glucose levels between acceptable limits, is 200 µg once a day. Because of that, the amount per serving of chromium in CORTI Support is 200 µg, as chromium picolinate.

The amount per serving of 200 µg for chromium in CORTI Support was compared to the amounts in the total population of dietary supplements in the U.S. The findings showed that the content of chromium in CORTI Support is above the median. (See figure 8) (NIH Office of Dietary Supplements, 2015)

Other studies, including a systematic review of 41 randomized controlled trials, (Balk, Tatsioni, Lichtenstein, Lau, & Pittas, 2007) support the use of chromium supplementation in diabetes.

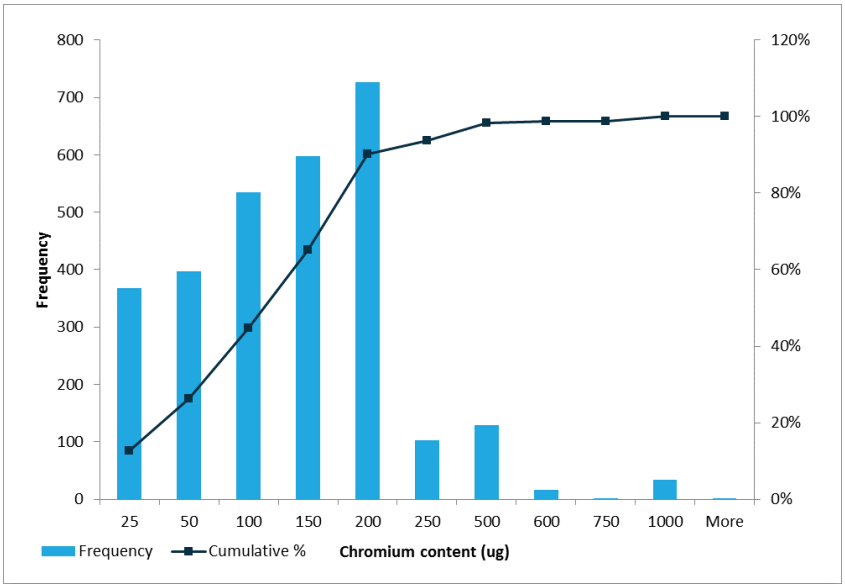

Figure 8. Chromium content in dietary supplements in the U.S. (unidose dosage forms)

7.7. L-valine + L-Leucine

The mixture of L-valine + L-leucine + L-isoleucine (Branched chain amino acids) which help maintain healthy muscles

The proportion 2:1:1 L-leucine : L-isoleucine : L-valine is used in all the products containing BCA.

8. FACTS AND CLAIMS

8.1. Facts

- Prolonged high-dose glucocorticoids therapy, decrease bone formation and increase bone resorption, which may lead to osteoporosis.
- Long-term use of oral glucocorticoids, especially at high doses, may cause steroid myopathy.
- Long-term use of oral glucocorticoids, especially at high doses, may cause hyperglycemia.

8.2. Claims

- Helps build strong bones & may help prevent osteoporosis.
- Helps maintain healthy muscles.
- Support healthy blood sugar levels.

9. PATENT PROTECTION

The patent application was submitted to the USPTO.

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