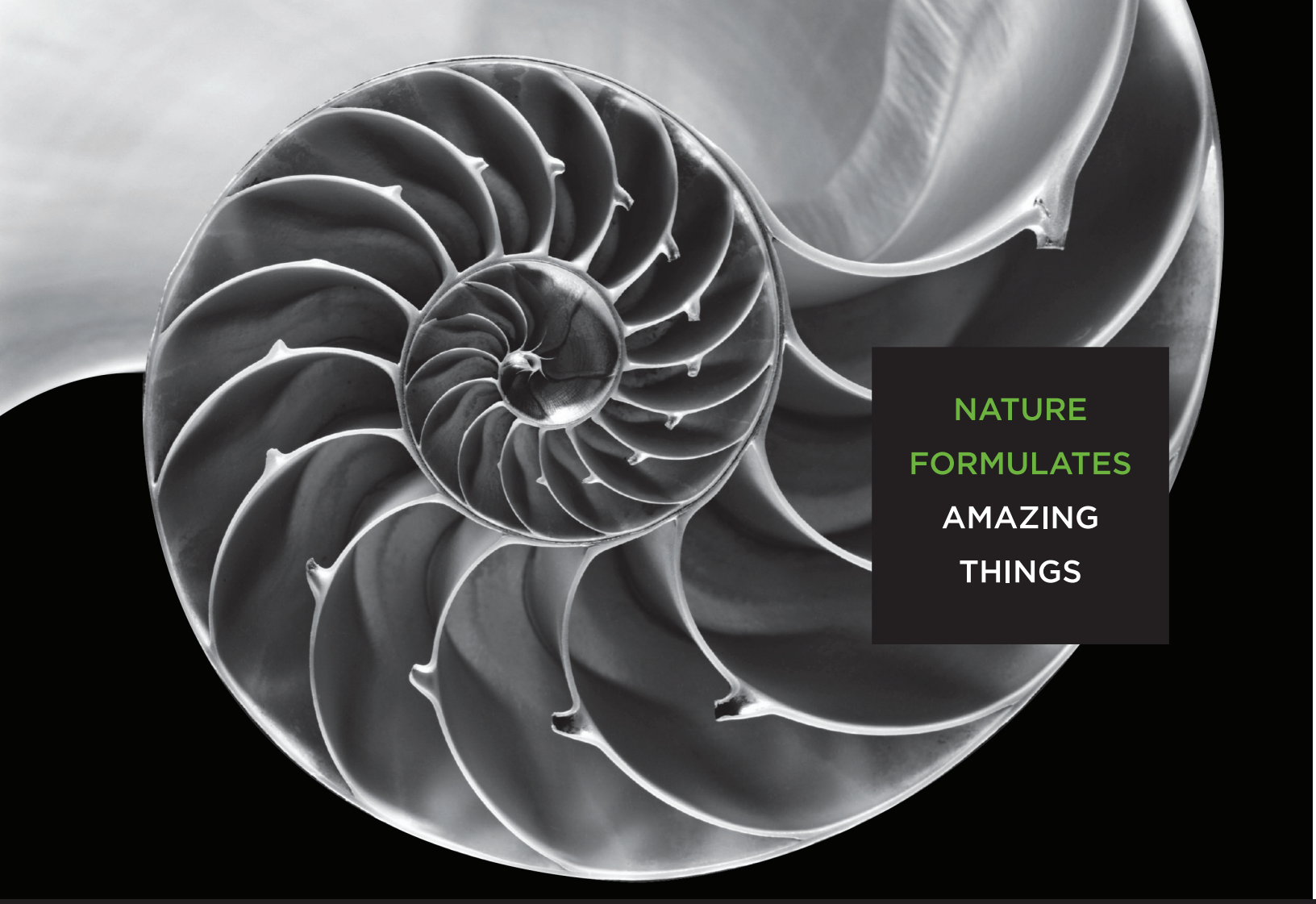

GLUCO BENEFITS™

DaVinci® BENEFITS line

SIMPLY FORMULATED
TO DELIVER MORE

METABOLIC HEALTH WITH GLUCO BENEFITS™

BALANCE IS ESSENTIAL

Metabolic health is an intricate puzzle dependent on the balance of our energy system. Think of energy production and use as an equation. When the equation is balanced, we see overall metabolic health result. Insulin sensitivity, nourishment, hormonal health and glycation levels are invaluable components of the equation.

As metabolic health remains a topic of extreme importance and relevance for your patients, understanding the above factors can help you develop the best lifestyle recommendations for every individual's needs.

This paper will discuss glycation, liver health and hormonal health -- and their respective impacts on insulin sensitivity -- as well as nutritional factors that may help support multiple areas of metabolic health.*

FACTORS ASSOCIATED WITH NORMAL METABOLISM:

A waistline that measures less than 35 inches for women, and 40 inches for men
Normal triglyceride levels
Normal HDL cholesterol levels
Normal blood pressure
Normal fasting blood sugar levels

GLYCATION

Glycation occurs when a protein or lipid molecule binds with a sugar molecule like glucose or fructose without the necessary moderating action of an enzyme. When an enzyme is present, glycosylation (a process necessary for molecular function) occurs; without it, glycation results, forming rogue molecules called advanced glycation endproducts. These endproducts (AGEs), are connected to a number of biological processes, such as the antioxidant system and the formation of reactive oxygen species (Tan et al., 2006).

Additionally, high levels of AGEs can deplete levels of nitric oxide, thereby creating vascular damage and setting the stage for heart concerns. In short, endogenous glycation is one of the major molecular processes that causes an accrual of damage.

It has been shown that lower levels of AGEs support nerve, eye and kidney health, three common metabolic systems. In addition, oral AGEs have been shown to promote insulin resistance by depleting antioxidant defenses of AGE receptor-1 and sirtuin-1. It is widely suspected that glucose, via glycation, is the primary damaging molecule in the aging body (Suji & Sivakami, 2004).

GLYCATION AND INSULIN SENSITIVITY

It's important to discuss glycation when we examine the body's metabolic health because AGEs may contribute to insulin resistance by a variety of mechanisms, including:

Generation of tumor necrosis factor (TNF)
Direct modification of the insulin molecule
Oxidative stress
Impairment of mitochondrial function

AGE receptor interaction perpetuates both AGE formation and cellular stress. It does so by inducing inflammation, oxidative stress, and a reduction in the expression and activity of the enzyme glyoxalase I. Glyoxalase 1 detoxifies the AGE precursor, methylglyoxal.

The glycation-promoting mechanisms may further stimulate AGE production and reduce insulin responsiveness by targeting tissue stresses (Song & Schmidt, 2012). Therefore, any consideration of support for normal rates of AGE formation may be beneficial in addressing overall insulin sensitivity.

GLYCATION AND NERVE HEALTH

Glycation end products can disrupt function in many tissues, including nerves (Brownlee, 2001; Feldman, 2012; Morales-Vidal, Morgan, McCoyd, & Hornik, 2012).

According to a 2008 study in Current Pharmaceutical Design, "Although the precise mechanisms underlying diabetic neuropathy remain unclear, there is evidence that hyperglycemia-induced formation of advanced glycation end products (AGEs) is related to diabetic neuropathy; AGE-modified peripheral nerve myelin is susceptible to phagocytosis by macrophages and contributes to segmental demyelination; modification of major axonal cytoskeletal proteins such as tubulin, neurofilament, and actin by AGEs results in axonal atrophy/degeneration and impaired axonal transport; and glycation of extracellular matrix protein laminin leads to impaired regenerative activity in diabetic neuropathy" (Sugimoto, Yasujima, & Yagihashi).

Another possible mechanism is binding: AGEs can trigger a cytokine response by binding to nerve cell surfaces (Vincent, Callaghan, Smith, & Feldman, 2011).

LIVER HEALTH

Given the emergence of understanding surrounding the glycemic index, high glycemic foods have earned a negative status with regard to health. In 2007, researchers from Children's Hospital Boston demonstrated a clear relationship (in mice) between consuming carbohydrates with a high glycemic index and the development of fatty liver.

According to Scribner, Pawlak and Ludwig, "A diet high in RAC causes accumulation of fat in liver, adipose tissue, and plasma in mice. Therefore, a low glycemic index diet may help prevent or treat NAFLD in humans" (Scribner, Pawlak, & Ludwig, 2007). It appears that the primary mechanism behind the damage caused by a high-glycemic diet is actually increased insulin production. The study also found higher plasma levels of insulin in mice fed the high-glycemic diet compared to those fed the low-glycemic diet (Cutler, 2007).

These results reveal the causal nature of the diet's impact on insulin, and remind us that healthy nourishment is an important factor in metabolic health. Further, these results bring to light the value of the liver in the conversation about insulin and metabolic health.

The liver both stores and manufactures (depending on need) the body's glucose and helps keep circulating levels steady. The signal to release or store comes from insulin or glucagon respectively. When the body is taking sugar in (during mealtime), glucose should be stored as glycogen. When the body needs to produce glucose (overnight, for example), the liver can either convert glycogen to glucose or produce glucose from fat byproducts, waste products and/or amino acids (Nolte Kennedy, Bedrich, White Gray, Kroon, & Demetsky, 2015).

The liver, whose function is so greatly affected by refined carbohydrate consumption, is also the site for much of the estrogen metabolism that occurs in the human body. The deep connections between the liver and the endocrine system tell us that metabolic health and insulin sensitivity support regimens should include support for healthy liver function--and for hormonal balance, as well.

HORMONAL BALANCE

Insulin's status as a hormone tells us how important the endocrine system is to healthy insulin sensitivity. Beyond insulin there exists an intricate web of hormones directly linked to metabolism, insulin sensitivity and peripheral nerve function.

Glucagon, which is released between meals and overnight, helps maintain sugar balance by signaling the liver to break down its stores. After a meal when the liver no longer needs to make sugar (the food sugar is introduced), glucagon levels drop. In people with metabolic challenges, glucagon levels rise

after a meal. GLP-1 (glucagon-like peptide-1), GIP (glucose-dependent insulinotropic polypeptide) and amylin, three other hormones, help regulate mealtime insulin. These hormones participate in decreasing glucagon levels, thereby decreasing the liver's mealtime sugar production, preventing levels from skyrocketing (Nolte Kennedy, Bedrich, White Gray, Kroon, & Demetsky, 2015).

Three other hormones still, epinephrine, cortisol and growth hormone, also help maintain blood sugar levels. Simply put, these "stress" hormones make blood sugar rise.

Epinephrine (adrenaline) does this through acting directly on the liver and through promoting fat nutrient breakdown. Those nutrients travel to the liver for conversion. Cortisol, also secreted from the adrenal gland, is incredibly important in our discussion of metabolism. It enhances glucose production by the liver and contributes to fat and muscle cell resistance to insulin. In a healthy body, cortisol works to counterbalance insulin action. In a stressed condition, it may become elevated to the point that insulin resistance could develop as a result.

Growth hormone comes from a different gland - the pituitary. Like cortisol, it acts as a counterbalance to insulin's effect. And, as is also true of cortisol, elevated levels of growth hormone may cause resistance to insulin's action.

Still another hormone, thyroid hormone, may also play a role in metabolic health through regulation of insulin's effect on adipose tissue (Arner, Bolinder, Wennlund, & Ostman, 1984).

NUTRIENTS TO SUPPORT METABOLIC HEALTH

Gluco Benefits™ represents a three-pronged approach to metabolic support:

- Botanicals to support healthy glucose levels*
- Nutrients to support normal insulin sensitivity*
- B vitamins to support healthy nerve innervation*

Glucevia, the fruit and seeds of *Fraxinus excelsior L.* (commonly known as the Ash), has long been used, just like Ash Bark and leaves, for medicinal purposes. In recent years, researchers have found its properties are supportive of metabolic health. In one human study, researchers concluded that "The administration of an extract from Fraxinus excelsior L. seeds/fruits in combination with a moderate hypocaloric diet may be beneficial in metabolic disturbances linked to impaired glucose tolerance, obesity and insulin resistance, specifically in older adults" (Zulet et al., 2014).

Another study published in 2015 found that, after seven months of administration, Glucevia supported insulin sensitivity while reducing fatty liver in-diabetic mice. The liver of supplemented mice presented 54% fewer fat droplets than the control group. This demonstrates that non-alcoholic steatosis in the liver was markedly reduced in treated mice thanks to Glucevia ("New study suggests preventive effect of Glucevia on liver damage," 2015).

GlucodOX®, a combination of a *Commiphora mukul* (guggul) extract and a medium-chain triglyceride (MCT) oil composed of C8 and C10 fatty acids, is a well-researched ingredient to support healthy lipid and glucose metabolism.

In one study, four groups of rats were treated with C. mukul gum resin ethanolic extract (CMEE) for 60 days. The "diabetic rats showed increased level of enzymatic activities aspartate aminotransaminase (AST), alanine aminotransaminase (ALT) in liver and kidney and oxidative markers like lipid peroxidation (LPO) and protein oxidation (PO) in pancreas and heart. Antioxidant enzyme activities were significantly decreased in the pancreas and heart compared to control group. Administration of CMEE (200 mg/kg bw) to diabetic rats for 60 days significantly reversed the above parameters towards normalcy," leading the researchers to conclude that the plant may be of use as an adjuvant therapy to support oxidative and glucose balance (Ramesh et al., 2012).

GlucodOX's action may support normal insulin sensitivity, cholesterol levels within normal ranges, regulate pre-adipoctye to adipocyte transformation balance, and support healthy glucose transport based on AMPK activity stimulation* ("GlucodOX™ - Natural metabolic support*," 2013).

Benfotiamine is a fat-soluble form of vitamin B1 that also supports glucose balance and addresses glycation through helping to protect the body's tissues from AGEs. Vitamin B1, or thiamin is known for its support of normal nerve health and function.* A required cofactor in the production of certain enzymes (such as those involved in glucose metabolism pathways), thiamin is critical for healthy metabolic function. **BenfoPure** is a benfotiamine formulation, an analog of thiamin.

As a lipid-soluble compound, it is both more ready for use and more active than traditional forms of thiamin. Benfotiamine is absorbed through the intestinal mucosa, then converted to its biologically active form, thiamin. Researchers have found that peak plasma concentrations of this form are at least five times greater after oral benfotiamine administration than the concentrations observed when water-soluble thiamine salts were administered ("Benfotiamine," 2006).

Relative to glucose metabolism, benfotiamine supports healthy transketolase activity, thereby blocking certain molecular pathways that may lead to hyperglycemic concerns.* Further, it supports the health of pathways that address the formation of AGEs.* Benfotiamine also supports eye health through supporting normal, healthy activation of NF-B in the diabetic retina.* Through supporting normal cell replication rates and healthy apoptosis, benfotiamine can also support the healthy of endothelial cells* ("Benfotiamine," 2006).

R-alpha lipoic acid supports both normal macronutrient metabolism and insulin utilization and offers free radical scavenging support to address glycation.* Importantly, it helps support and restore healthy intracellular glutathione levels.* The Linus Pauling Institute writes: "R-LA is the isomer that is synthesized by plants and animals and functions as a cofactor for mitochondrial enzymes in its protein-bound form. Direct comparisons of the bioavailability of oral LA and R-LA supplements have not been published. After oral dosing with LA, peak plasma concentrations of R-LA were found to be 40%-50% higher than S-LA, suggesting R-LA is better absorbed than S-LA" ("Lipoic Acid | Linus Pauling Institute | Oregon State University," n.d.).

Chromium at a relevant dose is key to any glucose support product.* When insulin binds to its receptor, chromium assists in the message and is then excreted from the cell, a process which appears to occur in a glucose-dependent manner, meaning that higher sugar means greater insulin binding, which means greater loss of chromium. The idea that chromium may be an appropriate support agent for people who experience glucose concerns is supported by findings that blood chromium levels are lower in people with metabolic challenges than in those without ("Scientific review: the role of chromium in insulin resistance," 2004). Supplementing with Chromium can help the body to build lean muscle mass, maintain glucose and cholesterol levels within normal ranges, and metabolize fat more efficiently.*

SUPPLEMENT FACTS

Serving Size 3 Capsules
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin B6 (as Pyridoxal-5-Phosphate)	55 mg	2,750%
Chromium (as Cr Polynicotinate)	1,000 mcg	833%
Glucevia® (Fraxinus excelsior)	1,000 mg	*
GlucoDox®	200 mg	*
R-alpha lipoic acid	100 mg	*
BenfoPure® Benfotiamine	75 mg	*

*Daily Value not established.

Other ingredients: microcrystalline cellulose, hypromellose (capsule), vegetarian leucine.

glucevia®
Glucose regulation begins here

MADE WITH NON GMO INGREDIENTS

Glucevia® is a registered trademark of Naturex.
GlucoDox® is a registered trademark of Dharma Biomedical LLC.

*These materials have not been reviewed by the U.S. Food and Drug Administration (FDA). This product is not intended to diagnose, treat, cure or prevent any disease. These materials are for physician education purposes only. Not for consumer distribution. www.davincilabs.com.

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