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- (71) Applicant (for all designated States except US): **AKESIS PHARMACEUTICALS, INC.** [US/US]; Suite B, 10555 Science Center Drive, San Diego, CA 92121 (US).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **FINE, Stuart, A.** [US/US]; 2230 White Oak Drive, Northbrook, IL 60062 (US).
- (74) Agents: **TAFT, Kingsley, L.** et al.; Foley, Hoag & Eliot, LLP, One Post Office Square, Boston, MA 02109 (US).
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(54) Title: COMBINATION OF CHROMIUM AND VANADIUM FOR GLUCOSE METABOLISM DISORDERS

(57) Abstract: Compositions and supplements, methods of using the same, and programs thereof, for the treatment and prevention of diabetes, other disorders of glucose metabolism, and other disorders or conditions are provided. Subject compositions may include, for example, a bioavailable source of chromium and a bioavailable source of vanadium.

COMBINATION OF CHROMIUM AND VANADIUM FOR GLUCOSE METABOLISM DISORDERS

Introduction

5 Diabetes adversely affects the way the body uses sugars and starches which, during digestion, are converted into glucose. Diabetes mellitus is generally caused by diminished rates of secretion of insulin by the beta cells of the islets of Langerhans in the pancreas, or by reduced insulin sensitivity. Insulin, a hormone produced by the pancreas, makes the glucose available to the body's cells for energy. In muscle, adipose (fat), and connective tissues, insulin facilitates the
10 entry of glucose into the cells by an action on the cell membranes. The ingested glucose is normally converted in the liver to CO₂ and H₂O (50%); to glycogen (5%); and to fat (30-40%), the latter being stored in fat depots. Fatty acids from the adipose tissues are circulated, returned to the liver for re-synthesis of triacylglycerol and metabolized to ketone bodies for utilization by the tissues. The fatty acids are also metabolized by other organs.

15 The net effect of insulin is to promote the storage and use of carbohydrates, protein and fat. Insulin deficiency is a common and serious pathologic condition. Diabetes is commonly divided into two types: Type 1 diabetes (juvenile-onset, insulin-dependent diabetes mellitus [IDDM]) that usually, but not always, begins in early life, and Type 2 diabetes (maturity-onset diabetes, non-insulin dependent diabetes mellitus [NIDDM]) that usually, but not always, begins
20 in later life. In Type 1 diabetes, the pancreas produces little or no insulin, and insulin must be injected daily. In Type 2 diabetes, the pancreas retains the ability to produce insulin and in fact may produce higher than normal amounts of insulin, but the amount of insulin is relatively insufficient, or less than fully effective, because of cellular resistance to insulin. Type 2 diabetes may present as non-obese NIDDM, obese NIDDM, or maturity-onset diabetes of the young
25 (MODY). Type 1 is likely to occur in those with a family history of diabetes and is characterized by blurred vision, itching, unusual thirst, drowsiness, obesity, fatigue, skin infections, slow healing, and tingling or numbness in the feet.

Type 1 Diabetes

Type 1 diabetes accounts for around ten percent of all cases of diabetes mellitus. The action of Type 1 diabetes is to cause hyperglycemia (elevated blood glucose concentration) and a tendency towards diabetic ketoacidosis (DKA). Currently, treatment requires chronic administration of insulin. No single standard exists for patterns of administration of insulin and treatment plans vary and may be selected from one of three treatment regimens: conventional, multiple subcutaneous injections, or continuous subcutaneous insulin infusion. Conventional insulin therapy involves the administration of one or two injections a day of intermediate-activity insulin such as zinc insulin or isophane insulin with or without the addition of small amounts of regular insulin. Regular insulin has a duration of action lasting from three to eight hours, whereas other forms of insulin are absorbed slowly from the injection site and therefore have effects that may last as long as ten to forty-eight hours. The multiple subcutaneous insulin injection technique involves administration of intermediate- or long-acting insulin in the evening as a single dose together with regular insulin prior to each meal. Continuous subcutaneous insulin infusion involves the use of a small battery-driven pump that delivers insulin subcutaneously into the abdominal wall, usually through butterfly needle. Insulin is delivered at a basal rate continuously throughout the day, with increased rates programmed prior to meals. Insulin may also be delivered by way of an implant that is administered parenterally, or by way of slow-release formulations.

Type 2 Diabetes

Type 2 diabetes is marked by hyperglycemia that is not linked with DKA. Sporadic or persistent incidence of hyperglycemia may be controlled by administering insulin. Uncontrolled hyperglycemia may transiently adversely affect the insulin-producing cells of the pancreas (the beta-islet cells), which may eventually result in greater insulin deficiencies. In most Type 2 diabetic subjects, the fundamental defects to which such abnormalities may be traced include (1) a reduced entry of glucose into various "peripheral" tissues, and (2) an increased liberation of glucose into the circulation from the liver. Consequently, there is an extracellular glucose excess and an intracellular glucose deficiency. There is also a decrease in the entry of amino acids into muscle and an increase in lipolysis. The cumulative effect of these diabetes-associated abnormalities may be severe blood vessel and nerve damage. Type 2 diabetic subjects may be treated with insulin, if necessary.

Type 2 often develops in subjects of certain at risk populations. Obesity predisposes an individual to Type 2 diabetes due to long-term effects on insulin resistance. Other populations thought to be at risk for developing Type 2 diabetes are the elderly; certain minorities; persons with Syndrome X; persons with concomitant hyperinsulinemia; persons with insulin resistance
5 characterized by hyperinsulinemia and by failure to respond to exogenous insulin; and persons with abnormal insulin and/or evidence of glucose disorders associated with excess circulating glucocorticoids, growth hormone, catecholamines, glucagon, parathyroid hormone, and other insulin-resistant conditions.

10 *Treatment of Diabetes and its Complications*

Diabetes has become a leading health care issue in the United States and other countries, accounting for one seventh of the entire U.S. health care budget. The incidence of diagnosed diabetes has increased five-fold in America over the past 35 years, with currently 8 million diagnosed diabetic patients, another estimated 8 to 12 million undiagnosed diabetic individuals,
15 and still an additional 23 million Americans with pre-diabetes, or impaired glucose tolerance (IGT). As the American populace continues its trend towards aging, obesity, and greater minority representation, the numbers of individuals who are diabetic or suffer from other glucose metabolism disorders is likely to increase.

20 *Diabetic Complications and Symptoms*

Although progress has been made in reducing the short term complications of diabetes, e.g. ketoacidosis, dehydration, and non-ketotic hyperosmolar coma, less progress has been made in preventing or minimizing the chronic complications of the disease, e.g. premature atherosclerosis, retinopathy, nephropathy, and neuropathy. For instance, it is estimated that a
25 diabetic patient's life is shortened by 10 to 15 years, and those years of life are distinguished by significantly increased medical care costs as compared to a non-diabetic patient. Some complications of diabetes include blindness and end-stage renal disease.

Another complication of diabetes mellitus is diabetic neuropathy (also called neuritis), which has been an unusually refractive complication of diabetes. Endoneural hypoxia is the
30 overt cause of diabetic neuropathy. Early symptoms include numbness, irritation, and pain, usually in the extremities, and more advanced ones include gastroparesis and impotence. The conversion of the essential fatty acid (EFA) linoleic acid to gamma-linolenic acid (GLA) appears

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to be impaired in diabetics because of a lack of the enzymes delta-6-desaturase and/or delta 5-desaturase. Consequently, there is shortage of GLA and its metabolites, prostacyclin and prostaglandins, the chronic deficiencies of which may contribute to the pathogenesis of diabetic neuropathy. Prostacyclin (PGI₂) is a vasoprotective molecule with multiple physiological functions, and the enzyme cyclooxygenase (cox) is involved in its synthesis. Two isoforms of cox have been identified to date: cox-1, which produces both prostacyclin and anti-inflammatory prostaglandins, and cox-2, which produces both thromboxane A₂ (TxA₂) and some of the prostaglandins responsible for inflammation. Many therapeutics for pain management inhibit both cox-1 and cox-2, thereby reducing inflammation caused by prostaglandins produced by cox-2, but also inhibiting production of prostacyclin, which may exacerbate a prostacyclin deficiency resulting in neuropathy. In addition, neurotrophic factors, such as the superfamily of neurotrophins including nerve growth factor, may present an alternative pathogenic mechanism that results in neuropathy.

Another complication of diabetes is increased cardiovascular risk factor, especially among women. A man's risk of dying by heart disease doubles upon developing diabetes, whereas a woman's risk increases three to five-fold.

In particular, Type 2 diabetes presents a number of co-existent cardiovascular metabolic risk factors, e.g., insulin resistance, hyperinsulinemia, central obesity, hypertriglyceridemia, low HDL level, quantitatively abnormal LDL (diabetic dyslipidemia), hypertension, glucose intolerance, and elevated blood pressure. This state has been identified as "Syndrome X." These cardiovascular risk factors may precede the onset of diabetes by as much as a decade, and they may explain the presence of overt clinical cardiovascular disease in as many as 60% of newly diagnosed diabetic patients. For example, elevated glycated hemoglobin (HbA_{1c}) is believed to be a risk marker for short-term mortality following acute myocardial infarction in non-diabetic subjects.

Diabetic dyslipidemia is another complication of diabetes and is of import to cardiovascular health. Plasma cholesterol and triglycerides are transported in lipoproteins (HDL, VLDL, and LDL). Dyslipoproteinemias are conditions in which the concentration and composition of these cholesterol- or triglyceride-carrying lipoproteins are abnormal. Elevated concentration of lipoproteins LDL and VLDL may accelerate the development of atherosclerosis, with the secondary possibilities of thrombosis and infarction. Evidence suggests that reduction of the concentration of lipoproteins LDL and VLDL in plasma may diminish the increased risk

of atherosclerosis that accompanies hyperlipoproteinemia. Dyslipoproteinemias have been designated as either primary or secondary. Secondary dyslipoproteinemias involve complications of a more generalized metabolic disturbance, such as diabetes mellitus or excessive intake of ethanol. In contrast, primary dyslipoproteinemias are typically caused either
5 by an inherited single-gene defect (monogenic dyslipoproteinemias) or a combination of multiple subtle genetic factors that act together with environmental ones (multifactorial or polygenic dyslipoproteinemias).

Evidence suggests that treatment of hyperlipoproteinemia may diminish or prevent atherosclerotic complications. For example, populations studies have shown that an elevated
10 concentration of total cholesterol or LDL-cholesterol in plasma constitutes a major risk factor for the occurrence of atherosclerotic events. In the case of monogenic disorders, family studies have documented a markedly increased risk of vascular disease among affected members. These is evidence that reduction in plasma concentrations of LDL-cholesterol may reduce the risk of coronary heart disease (CHD).

Furthermore, there may be an excessive risk of cardiac mortality in diabetic patients even after adjusting for the co-existence of other cardiovascular risk factors such as hypertension, dyslipidemia, and cigarette smoking. This increase risk of cardiac mortality is secondary to both the atherogenicity of insulin resistance, which may precede the onset of diabetes by at least 8 years, and the atherogenicity of undiagnosed and uncontrolled hyperglycemia, which may be
20 present for 9-12 years before diabetes is first diagnosed.

One means of attenuating the cardiovascular effects of diabetes, would involve earlier diagnosis and improved management of diabetes to reduce insulin resistance and to control blood glucose. To this end, screening for risk factors for vascular complications followed by appropriate treatment may be appropriate.

Because of the many complications that accompany diabetes and other glucose metabolism disorders, there remains a need both to improve treatment methods presently available and to devise new means of treatments for preventing the on-set and reducing the severity of Type 1 and 2 diabetes and other glucose metabolism disorders. In part, the present invention provides compositions, methods for using them, and programs thereof, that have been
30 observed to alleviate or prevent glucose metabolism disorders, such as diabetes, and associated sequelae.

Summary of the Invention

The present invention represents new and important treatments or nutritional regimes for maintaining or promoting health, including the treatment of diabetes, pre-diabetics and the reduction or avoidance of the onset of diabetes.

5 In certain embodiments, the present invention provides compositions and supplements, and methods of using the same, for preventing, reducing or treating in animal subjects (including humans and other mammals) one or more of the following physiological conditions: insulin resistance (the sensitivity of the cellular response of a species to insulin), beta cell attrition, hyperinsulinemia, hyperglycemia, hepatic glucose neogenesis, onset of diabetes or diabetic
10 symptoms, elevated HbA1c levels, and elevated or inappropriately controlled blood glucose levels. In certain embodiments, the present invention abates, or otherwise reduces the severity of, diabetes and other glucose metabolism disorders, including Type 1, Type 2, MODY, and IGT, and any related sequelae, including, for example, obesity, obesity-related hypertension, retinopathy, nephropathy, neuropathy, cataracts, coronary artery disease and arteriosclerosis. In
15 other embodiments, the present invention provides supplements or compositions, and methods of using the same, for regulating, modulating or altering glucose metabolism in a manner beneficial to the patient. Generally, various embodiments of the invention may be applied or tailored to specifically treat or address each condition described herein and others like them, including any condition or disorder related to glucose metabolism disorders.

20 In other embodiments of the present invention, supplements and compositions, and methods of using the same, are provided to modulate at least one of body fat stores, blood pressure, hyperlipoproteinemia, hypertriglyceridemia, serum cholesterol level, HDL level, and LDL level. In certain embodiments, the present invention abates or otherwise reduces the severity of dyslipidemia, atherosclerosis and CHD. In other embodiments, the present invention
25 provides supplements or compositions, and methods of using the same, for regulating, modulating or altering lipid metabolism in a manner beneficial to the patient. In still other embodiments, the present invention provides compositions and supplements, and methods for using the same, to reduce appetite for cosmetic purposes or treatment of illness, dysfunction or obesity.

30 In certain embodiments, the invention compositions include at least a therapeutically effective amount of a bioavailable source of chromium and a bioavailable source of vanadium. In addition, embodiments of the present invention may include any of the other components set

forth herein and others known to those of skill in the art, including any agents, components or ingredients that are beneficial in the treatment or prevention of glucose metabolism disorders or any sequelae related to such disorders.

In some instances, the present invention is designed to regulate any of the physiological processes described herein so as to achieve a desired level of a physiological parameter (e.g., a HbA1c level of about 5%), which may result in an appreciable improvement in the level. In certain embodiments, such a result is accomplished without subjecting a patient to elevated levels of such a parameter. Still other embodiments of the invention are particularly preferred in preserving health or reducing, preventing or delaying the onset of diabetes or diabetic symptoms without the patient experiencing the full thrust of such medical conditions. Some of these aspects of the invention may be particularly helpful in preventive care regimes.

In one embodiment of the present invention, a number of patients that presented with an elevated level for HbA1c ingested one embodiment of the present invention over a three month period. HbA1c is one means of assessing the state of an individual's glucose metabolism over a several month period. In general, a desirable HbA1c level is less than 7%, and less than 6% is generally considered non-diabetic. Usually, medical intervention is called for if a subject's HbA1c level exceeds 8%. The average HbA1c levels of the ten individuals before the program was 9.40%, and the range was 12.7 to 8.1%. After approximately ninety days of ingesting a supplement of the present invention, the average HbA1c level for the ten individuals was 7.29%, and the range was 8.9 to 5.7%. This program therefore resulted in an average drop of 2.11% in HbA1c levels, and the HbA1c levels for eight of the ten subjects was reduced below 8%.

It is yet another object of this invention to provide supplements or compositions, and methods of using the same, for the long-term reduction and abatement of at least one of the foregoing disorders or conditions based on a therapeutic regimen administered over the short-term and/or long-term. In certain aspects, the present invention contemplates monitoring such disorders or conditions as part of any therapeutic regimen.

In another aspect of the present invention, the subject compositions or supplements may be used in the manufacture of a medicament to treat any of the foregoing conditions or diseases. In certain embodiments, the present invention is directed to a method for formulating compositions or supplements of the present invention in a pharmaceutically acceptable excipient. In still other embodiments, the present invention contemplates compositions or supplements of the present invention for the treatment any of the foregoing conditions or diseases.

In part, the present invention is directed to a dietary supplement that may be formulated for people individuals in an increased risk category as identified by any number of risk factors, including familial history.

In another embodiment of the invention it will be desirable to include monitoring or
5 diagnostic regimes or kits with composition or methods based on mineral and vitamins products described herein.

In other embodiments, the present invention contemplates programs for prevention or treatment of any of the foregoing disorders or conditions. In some embodiments of such programs, one or more physiological parameters will be measured, and dosing and/or
10 composition of supplement will be varied to reflect the health of the individual. Certain programs require that the patient ingest the supplement for a minimum time period, whereupon the same physiological parameters will be measured again to determine what affect the supplement may have caused. In certain embodiments, the programs call for changes in dosing, components, or formulation of the supplement depending on the results reported after an initial
15 trial period on a program. In certain embodiments, programs of the present invention may require monitoring by the patients or additional treatment or prevention activities, such as dietary recommendations or exercise suggestions. In addition, in certain instances, the programs may include instructions for the patients concerning the scope and purpose of the program.

20 **Detailed Description of the Invention**

1. Definitions

For convenience, before further description of the present invention, certain terms employed in the specification, examples, and appended claims are collected here. These
25 definitions should be read in light of the rest of the disclosure and understood as by a person of skill in the art.

The term "anti-diabetic" shall mean any composition or supplement, or method of using the same, that is useful in one or more of the following: treating, preventing, or otherwise reducing the severity of any glucose metabolism disorder, or any complications thereof,
30 including any of the conditions, disease, or complications described herein.

The term "bioavailable" means that a compound, composition, supplement, component, or material is in a form that allows for it, or a portion of the amount administered, to be absorbed

by, incorporated to, or otherwise physiologically available to a subject to whom it is administered. In certain embodiments of the present invention, bioavailable sources of components of supplements or compositions of the present invention containing a transition metal, including chromium, vanadium and others, are contemplated, as discussed in more detail
5 herein.

An embodiment of the invention is said to have an "insulinotropic activity" if it is able (i) to stimulate, or cause the stimulation of, the synthesis or expression of the hormone insulin, or (ii) to increase the half-life or the apparent potency of insulin in vivo. Insulin may be any naturally occurring form of the polypeptide, or any form of insulin, including any polypeptide
10 that achieves the same effect of insulin, administered to a patient.

The phrases "parenteral administration" and "administered parenterally" means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular,
15 intra-articular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The term "modulation" as used herein refers to up regulation (i.e., activation or stimulation), down regulation (i.e., inhibition or suppression) of a response, or the two in combination or apart.

The phrase "pharmaceutically acceptable" refers to those supplements, components,
20 materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically-acceptable carrier" as used herein means a
25 pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any supplement or composition, or component thereof, from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the supplement and not injurious to the patient. Some
30 examples of materials which may serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and

cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl
5 oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

The term "pharmaceutically-acceptable salts" refers to the relatively non-toxic, inorganic
10 and organic acid addition salts of components of compositions of the present invention.

The phrases "systemic administration," "administered systemically," "peripheral
administration" and "administered peripherally" mean the administration of a subject
supplement, composition, therapeutic or other material other than directly into the central
nervous system, such that it enters the patient's system and, thus, is subject to metabolism and
15 other like processes, for example, subcutaneous administration.

The phrase "therapeutically-effective amount" means that amount of supplement or
composition which is effective for producing some desired therapeutic effect. For example,
certain compositions of the present invention, or components thereof, may be administered in a
sufficient amount to modulate glucose metabolism at a reasonable benefit/risk ratio applicable to
20 such treatment.

2. General Introduction

The present invention provides methods and compositions for modification and
regulation of glucose and lipid metabolism, generally to reduce insulin resistance,
25 hyperglycemia, hyperinsulinemia, obesity, dyslipidemia, hyperlipoproteinemia (such as VLDL),
and to regulate body fat and more generally lipid stores, and, more generally, to improve of
metabolism disorders, especially those associated with diabetes, obesity, atherosclerosis, or
CHD.

For instance, in certain embodiments of the present invention, administration of a subject
30 supplement or composition, or methods of using the same, in an effective amount improves one
or more aberrant indices associated with glucose metabolism disorders (e.g., glucose intolerance,
insulin resistance, hyperglycemia, hyperinsulinemia, diabetic dyslipidemia, and Type 2 diabetes).

In other embodiments, administration of a subject supplement, or methods thereof, in an effective amount improves aberrant indices associated with CHD or obesity.

In other embodiments, the supplements and compositions have anti-diabetic activities, and may be used in the treatment of disorders marked by aberrant glucose metabolism (including storage). In certain embodiments, supplements or compositions, or components thereof, of the present invention are useful as insulin enhancing or insulinotropic agents. The subject compositions or methods may be useful for the treatment and/or prophylaxis of a variety of disorders, including one or more of dyslipidemia, hyperglycemia, obesity, glucose tolerance insufficiency or impairment, insulin resistance, and diabetic complications.

In certain embodiments, the invention compositions include at least a therapeutically effective amount of a bioavailable source of chromium and a bioavailable source of vanadium. In certain embodiments, the present invention is directed towards a supplement or composition containing one or more additional components from the following group: magnesium, vitamin E, aspirin; alpha-lipoic acid; and folic acid.

In one embodiment, a supplement includes an effective amount of chromium polynicotinate and/or chromium picolinate as the chromium source, an effective amount of vanadyl sulfate as the vanadium source, an effective amount of magnesium as either a complex of chloride or Krebs (citrate, fumarate, malate, glutarate and succinate complex), an effective amount of vitamin E as free 2R, 4'R, 8'R-alpha-tocopherol, an effective amount of aspirin as standardized willow bark, an effective amount of folic acid and alpha-lipoic acid, as well as sufficient amounts of other vitamin and mineral sources.

In another aspect, the present invention is directed to supplements or compositions capable of preventing, treating, or otherwise reducing the severity of disorders of glucose metabolism. Insulin resistance is the pathophysiologic indicator of patients with IGT and Type 2 diabetes, which often occurs many years before clinically evident disease is present. As peripheral glucose use decreases, subjects may remain euglycemic, but hyperinsulinemic, as long as beta cells maintain sufficient insulin concentrations. Eventually, insulin resistance and rising plasma glucose levels outpace insulin production. The disease or condition progresses from insulin resistance with hyperinsulinemia to impaired glucose tolerance, resulting in modest increases in post-prandial glucose concentrations, followed by clinical diabetes and hyperglycemia. The supplements and compositions of the present invention, and methods of

using the same, are intended to delay the onset of Type 2 diabetes and its associated sequelae by addressing disorders of glucose metabolism at an early stage.

The present invention also provides methods for enhancing the natural control of blood glucose levels in a person by daily administration of the subject composition and nutritional
5 supplement. The present invention contemplates administration of a supplement of the present invention to control the blood sugar by reducing insulin resistance in diabetic and IGT patients, thereby preventing the chronic complications from developing in these high risk patients. There is also a need to provide an effective supplement for the treatment of diabetes and its symptoms prior to the onset of full-blown diabetes.

10 In another aspect, the present invention also provides for kits containing at least one dose of a subject supplement or composition, and often many doses, and other materials for a treatment regimen. For example, in one embodiment, a kit of the present invention contains sufficient supplement for thirty days and equipment and supplies necessary to measure one or more indices relevant to glucose metabolism, such as blood glucose levels. In another
15 embodiment, kits of the present invention contain all the materials and supplies, including supplements and compositions, for carrying out any methods of the present invention.

In another aspect, the present invention provides for programs whereby the supplements or compositions of the present invention are ingested by a subject having a condition described herein, including subjects that are pre-diabetic. The program format of the present invention
20 allows for a variety of variables to be addressed in providing composition and supplements of the present invention. Some of these variables include: one or more conditions to be addressed by any one program, compositions and supplements to be used in any such program, and dosing regimen of any such program. In certain instances, a program may include a kit of the present invention.

25 Many of the features of any program, including for example the dosing regimen, may be provided for in instructions to the subject participating in any program. Such instructions may, in certain embodiments, require the subject to decide whether to continue any program depending on the results obtained while on the program. The length of such trial period may vary with the particular program. Typically, trial periods may be between about one to about six
30 or more months, and alternatively, the trial periods may be between one and three months.

In certain embodiments of such programs, the subject may be required to assess their progress on the program by monitoring a parameter relevant to their particular condition. In

certain embodiments, a program directed to prevention or treatment of a glucose metabolism disorders may require subjects to monitor their HbA1c levels. After a certain period on such a program, during which the subject would have used the composition or supplement prescribed by the program in the manner dictated thereby, the program may require the subject to determine
5 their HbA1c level. Depending on whether the HbA1c level changed by a particular amount, the subject may continue with the particular program, discontinue the program altogether, or alter the program. The foregoing decision may depend on the initial condition of the subject.

For example, in one embodiment of a program of the present invention, the dose of chromium administered to a patient in a composition varies with the initial HbA1c level.

10 Accordingly, in this particular example, the chromium dosages would be as follows: for a patient having an HbA1c level in the range of about 7 up to about 8, a dose of chromium is in the range of about 0.003 mg Cr or less/kg of body weight up to about 0.009 mg Cr or less/kg, for a patient having an HbA1c level in the range of about 8 up to about 9, a dose of chromium is in the range of about 0.005 mg Cr/kg of body weight up to about 0.01 mg Cr/kg of body weight, for a patient
15 having an HbA1c level in the range of about 10 up to about 11, a dose of chromium is in the range of about 0.006 mg Cr/kg of body weight up to about 0.015 mg Cr/kg of body weight, and for a patient having an HbA1c level in the range of at least about 11, a dose of chromium in the range of about 0.007 mg Cr/kg of body weight up to about 0.04 mg Cr or more/kg of body weight. The particular dose of chromium would be maintained for a trial period, whereupon the
20 HbA1c level would be measured again. If the patient's HbA1c level had dropped during the trial period, then the dose of chromium ingested could be reduced; if the HbA1c level had not decreased, the patient would have a number of options: the dose of chromium could be increased, the same dose could be ingested for a longer time period, or a different chromium complex with potentially differing bioavailability and potency for the particular individual could be used. This
25 program could be applied to any other component or ingredient of the present invention, including, for example, any vanadium containing complex.

In addition to those indices already discussed above, a number of parameters of blood serum may be measured to assess the efficacy of any supplement or method of the present invention in attending to the conditions described herein. Any of these parameters may serve as
30 the basis of a program of the present invention. Useful parameters include: LDL-cholesterol, HDL-cholesterol, apolipoprotein A1, apolipoprotein B, HbA1c, and blood sugar level (fasting, post-prandial and urine). It has been observed that the subject compositions are especially

effective in improving blood glucose control after eating, so the post-prandial measurement is preferred in certain programs of the present invention.

Other measurements of import for any subject invention include heart rate, blood pressure, weight, and temperature. To assess the present invention's affect on a patient's body condition, the following may be monitored: various skin-fold thicknesses, bicep and calf
5 circumferences, body weight, lean body mass, percent body fat, body mass index (BMI), and waist-to-hip ratio (WHP).

The amounts of the individual components of preparations of this invention may vary, although in certain preparations the components are present in amounts lying within certain
10 ranges presented herein. The present invention typically contemplates administering the dosages of any supplement or composition on a daily basis, or at other frequencies appropriate to the supplement or composition and its mode of delivery. For example, a dose of a composition of the present invention may be ingested or administered daily in a single serving, e.g., a tablet or a liquid, or in multiple servings. Alternatively, the dosages of the present invention may be
15 ingested over a several day period or over any other time period so as to achieve the desired therapeutic effects.

Certain supplements and compositions of the present invention contemplate components that are transition metal chelates. Certain of the metal chelates contemplated by the present invention may have, in addition to any chelating ligand or ligands that are bound covalently or
20 through ionic interactions to said metal ion, a counter-ion that is generally not bound to the metal ion (or if associated, only weakly so), and counters any charge of the metal-ligand complex. For example, in vanadyl sulfate hydrate, the sulfate would generally be considered a counter-ion to the vanadyl ion metal-ligand complex. Some examples of commonly encountered counter-ions include sulfate, perchlorate, nitrate, halogens, and the like. In addition, the metal chelates may
25 have a number of waters of hydration associated with them. For example, one form of magnesium dichloride is magnesium dichloride hexahydrate, in which six waters of hydration are part of the metal complex. A metal chelate that is identified as an hydrate may have one or more waters of hydration. In addition, the number of molecules of waters of hydration may be a non-integer number when expressed as a ratio of one molecule of metal complex to the molecular
30 number of the waters of hydration. One means of determining the numbers of water of hydration is by elemental analysis. In some instances, but not all, the number of waters of hydration may affect the bioavailability, water solubility and other properties of a metal complex.

In providing a dose of transition metal chelate to a subject, the most appropriate dose may depend, in part, on the nature of the metal chelate. Certain transition metal or mono- or multi-valent ion complexes may be more readily assimilated than others, and may therefore be more effective in achieving the desired therapeutic response than other complexes. Another important factor may be the water solubility of any metal complex. Another relevant factor may be the mode of administration. Consequently, dosages of the complexes typically contemplated by the present invention usually depend on the identity of the complex, the means of administration, and the formulation in which the complex is administered.

For instance, chromium picolinate appears to be absorbed at a rate about four times greater than chromium trichloride upon oral administration to rats. Usually, chromium picolinate is preferred over chromium trichloride as the administered complex. In other embodiments, chromium polynicotinate will be preferred over chromium picolinate as it contemplated that chromium polynicotinate will generally have better absorption and metabolic properties than chromium picolinate.

For many transition metal chelates (or other metal chelates), such as those contemplated by the present invention, the metal chelate or other inorganic complex administered to a subject may differ from the form that is responsible for any biological activity. Furthermore, many different complexes of the same transition metal may cause a biological response to different degrees. For instance, a transition metal complex may undergo any number of reactions in vivo, including: hydrolysis, which depends greatly on pH conditions; redox reactions, whereby the transition metal, or even a chelating ligand, may change electronic state, which depends greatly on the local redox environment; and other ligation reactions, whereby a molecule may, because of, for example, superior binding characteristics and/or affinity or greater concentration, displace a ligand chelating the metal. It is not uncommon for a transition metal complex, especially those containing first row transition metals, to undergo complete hydrolysis upon ingestion or administration to a subject and possibly chelation by a molecule present in vivo. Generally, complexed forms of such metals will be selected to direct or maintain the desired form of the metal in the body. Other potentially desirable characteristics in metal complexes include: a neutral charge to the complex, sufficient water solubility (e.g., capable of forming an at least a 0.1 mM solution); and capable of being absorbed orally and gastro-intestinally.

For the different transition metals that serve as components in the subject supplements, particular complexes are discussed in more detail herein. In addition, pharmaceutically

acceptable salts of such transition metals that may serve as components in the subject preparations generally include the conventional non-toxic salts of the compounds, e.g., salts derived from non-toxic organic or inorganic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, valeric, oleic, lauric, lactic, lactobionic, laurylsulphic, and the like. See, for example, Berge et al. J. Pharm. Sci. 66:1-19 (1977). For the different transition metal or other metal complexes of the present invention described herein, the dosages are presented with reference to the amount of elemental transition metal or other metal in such complex, unless otherwise expressly indicated or implied by the context.

Contemplated equivalents of the components of the subject compositions of the present invention include compounds or materials that otherwise correspond thereto, and which have the same general properties thereof, wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of the compound in the composition or in use in the contemplated method.

As explained herein in greater detail, the present invention readily enables the design and implementation of trials in warm-blooded animals, including humans and mammals, necessary for easily determining or tailoring the form and dose for any supplement, and the components thereof, of the present invention.

3. Exemplary Compositions and Methods of Using the Same

In certain embodiments, the nutritional supplements of the present invention may supplant other forms of diabetes and IGT treatment, such as appropriate diet and exercise or insulin. In certain embodiments, programs of the present invention require that the subject complement such treatment methods with the compositions of the present invention.

3.1 Components of Compositions or Supplements

In one embodiment of the present invention, it has been discovered that a dietary supplement containing effective amounts of metabolically available forms of vanadium,

chromium, magnesium, and vitamin E in combination with naturally available sources of aspirin, alpha-lipoic acid, and folic acid improves the metabolism of glucose. Such compositions may be also used to arrest, treat or otherwise reduce the severity of many of the cardiovascular complications or risk factors associated with diabetes or pre-diabetes. These components
5 perform different functions which, when administered in appropriate dosages and forms, typically enhance the metabolism of glucose

In part, the present invention contemplates combinations of components or ingredients in different supplements or compositions to produce a therapeutic effect in a patient with a glucose metabolism disorder, such as Type 2 diabetes, IGT, Syndrome X, insulin resistance, or
10 hyperinsulinemia. In general, the therapeutic effect may be measured by reference to any number of indices that are directly related to glucose metabolism, such as blood glucose level or HbA1c level, or other parameters that may otherwise be affected by such a disorder or a related condition or disease. The present invention teaches how to test supplements or compositions containing any one or more of the components set forth herein to determine whether any
15 particular combination of components in a supplement or composition results in a desirable therapeutic effect upon administration to a patient.

In certain embodiments, the subject compositions contain at least a therapeutically effective amount of a bioavailable source of chromium and a bioavailable source of vanadium. In other embodiments, the subject supplements consist essentially of the components indicated
20 for that particular supplement.

3.1.1 Chromium

Chromium is a trace mineral found in human tissues. Claims surrounding the use of chromium as a supplement, such as weight loss and building muscle mass, have been made for
25 non-diabetic individuals. Notwithstanding such claims, the status of chromium supplementation, even for diabetic patients, appears to be unsettled. Although chromium supplementation may be prescribed for individuals who are chromium deficient, the prevalence of chromium deficiency in diabetic patients appears to be difficult to establish.

Without limiting the invention to a particular mechanism of action, chromium at the
30 appropriate dosage and form may cause improved glucose or lipid metabolism by overcoming insulin resistance. Chromium may increase insulin binding to cells by increasing the number of

insulin receptors. Alternatively, chromium may increase insulin sensitivity by increasing insulin receptor phosphorylation.

The present invention contemplates metal complex of chromium in which the chromium is bioavailable. Some examples of such sources of chromium include chromium trichloride, chromium acetate, chromium nicotinate (or polynicotinate), chromium picolinate, chromium glycinate, chromium oxalate, chromium perchlorate, chromium salicylate, chromium nicotinate glycinate, chromium 4-oxo-pyridine-2,6-dicarboxylate, chromium chelidamate or arginate; and chromium tris-acetylacetonate. Another possible source of chromium is glucose tolerance factor, which contains chromium thought to be complexed as chromium nicotinate. Finally, in addition to those metal complexes specifically set forth herein, other salts and complexes of chromium known to those of skill in the art are contemplated by the present invention. As discussed generally above, the chromium complexes contemplated by the present invention may differ in bioavailability and potency.

The chromium complexes may contain chromium in the (III) (i.e., trivalent), (VI) (i.e., hexavalent), or other valent states, although it is believed that the trivalent state is responsible for biological effects of interest in the present invention and is therefore preferred. Chromium in many of the chromium containing complexes contemplated by the present invention typically have chromium in the (III) valency.

Certain embodiments of the present invention contemplate doses of chromium from about 100 mcg to about 5000 mcg or higher. Unless expressly provided otherwise, the dose amounts referred to herein refer to the amount of chromium in any particular form, such as complex or in any particular valency. By way of example, to provide 200 mcg of chromium using chromium trichloride, a patient would need to ingest about 610 mcg of chromium trichloride.

Particular dosages of chromium contemplated by the present invention include about 200 mcg, 300 mcg, 333 mcg, 500 mcg, 650 mcg, 750 mcg, 1000 mcg, 1250 mcg, 1500 mcg, 2000 mcg, 2500 mcg, 3000 mcg, 3500 mcg, 4500 mcg, and 5000 mcg, as well as other possible dosages determined by one of skill in the art. Higher dosages, while they may be daily dosages, may be used as short term regimes (e.g. less than about one month) and may taper into dosages in the lower end of the taught ranges. In certain instances, it may be advantageous not to fall below about 250 to 600 mcg of chromium per day when tapering the dose.

In certain embodiments, the dose of chromium may be modified if the supplement or composition contains a bioavailable source of vanadium. For example, the dose of chromium may be reduced by from about 10% to about 75%, or alternatively 25%, 33%, 55%, or 66%. The amount of reduction in the chromium dose may depend, in part, on the dose of vanadium
5 provided for in any supplement of the present invention, as well as the source of the vanadium and the means of administration.

For any of the components described herein, the dose may be varied as necessary, for example, to treat one or more specific conditions set forth herein, or for example, to reflect any differences in administration or the nature of the components employed in any particular
10 composition, method or program of the present invention. For example, the dose of chromium may be reduced as ingestion of the supplement results in improved blood glucose control. The patient may need to monitor a number of indices, such as blood glucose levels or HbA1c levels, to determine the appropriate dosing.

In additional embodiments of present invention, the dose of chromium is based on the
15 weight of the intended recipient. Accordingly, in one embodiment of the present invention, the dose of chromium is in the range of about 0.001 mg or less/kg of body weight up to about 0.06 mg or more/kg of body weight. In another embodiment of the present invention, the dose is at least about 0.01 mg/kg body weight. In still another embodiment of the present invention, the dose is in the range of about 0.002 mg/kg of body weight up to about 0.02 mg/kg of body weight.

20 In further embodiments of the present invention, the dose of chromium may be determined based on the intended recipient's condition. For example, in one embodiment, the dose of chromium may depend on the subject's HbA1c level. Accordingly, in this particular example, for a patient having an HbA1c level in the range of about 7 up to about 8, a dose of chromium is in the range of about 0.003 mg or less/kg of body weight up to about 0.009 mg or
25 less/kg, for a patient having an HbA1c level in the range of about 8 up to about 9, a dose of chromium is in the range of about 0.005 mg/kg of body weight up to about 0.01 mg/kg of body weight, for a patient having an HbA1c level in the range of about 10 up to about 11, a dose of chromium is in the range of about 0.006 mg/kg of body weight up to about 0.015 mg/kg of body weight, and for a patient having an HbA1c level in the range of at least about 11, a dose of
30 chromium in the range of about 0.007 mg/kg of body weight up to about 0.04 mg or more/kg of body weight. Dosing for a particular's subject condition may be based on any of the parameters known in the art or described herein useful for assessing the condition of any subject. For

example, a number of parameters of blood serum, in addition to HbA1c levels, may be used to determine appropriate dosing. Other measurements of import of potential use for dosing purposes are described herein.

Chromium in the trivalent state is one of the least toxic nutrients: the reference dose
5 established by the US EPA is 350 times the upper limit of the Estimated Safe and Adequate
Daily Dietary Intake (ESADDI) of 200 mcg per day, wherein the reference dose is defined as the
estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to a
human population, including sensitive subgroups, that is likely to be without appreciable risk of
deleterious effects over a lifetime. Consequently, the present invention contemplates doses of
10 trivalent chromium that substantially surpass the ESADDI but which may be necessary to
produce the greatest therapeutic effect.

3.1.2 Vanadium

In some embodiments, vanadium compounds of the present invention are believed to
15 have an insulin mimetic effect. Vanadium, often in the form of vanadate appears in certain
tissues to stimulate glucose transport, activate glycogen synthase, increase glycogen syntheses in
fat cells, and stimulate carbohydrate uptake in the liver like insulin.

A commonly used source of vanadate is vanadyl sulfate. Upon ingestion, vanadyl sulfate
is typically reduced to vanadate, which is a salt, of vanadic acid. Glycogen synthase is an
20 enzyme that causes the conversion of glucose into glycogen. Vanadate appears to activate
glycogen synthase in the same manner as insulin. For example, vanadate appears to have no
effect if insulin concentration is at a maximum, whereas if insulin is at less than maximum,
vanadate increases both glycogen synthase activation state and 2-deoxyglucose transport to the
level obtained if insulin were at maximized. Vanadate and insulin activate glycogen synthase
25 within similar time frames, and adrenaline partially reverses both vanadate and insulin activated
glycogen synthase. Also, insulin and vanadate counteract the activating effect of adrenaline on
glycogen phosphorylase.

Dosages of vanadium in compositions of the present invention range from less than 5 mg
to more than 100 mg. Unless expressly provided otherwise, the dose amounts referred to herein
30 refer to the amount of vanadium in any particular form, such as any particular complex or in any
particular valency.

Particular dosages of vanadium contemplated by the present invention include about 0.1 mg, 1 mg, 5 mg, 10 mg, 20 mg, 25 mg, 50 mg, 75 mg, 100 mg, and 125 mg. In certain embodiments, the amount of vanadium administered is about 5 mg to 50 mg. Typically, these are daily dosages. Higher dosages, while they may be daily dosages, may be used as short term regimes (e.g. less than about one month) and may taper into dosages in the lower end of the taught ranges.

In certain embodiments, it may be useful to represent the preceding doses may be in terms of vanadyl (VO^{2+}) instead of vanadium. Such dosages would be: 0.1 mg V, 0.13 mg VO^{2+} ; 1 mg V, 1.3 mg VO^{2+} ; 5 mg V, 6.55 mg VO^{2+} ; 10 mg V, 13.1 mg VO^{2+} ; 20 mg V, 26.2 mg VO^{2+} ; 25 mg V, 32.8 mg VO^{2+} ; 50 mg V, 65.5 mg VO^{2+} ; 75 mg V, 98.3 mg VO^{2+} ; 100 mg V, 131 mg VO^{2+} ; and 125 mg V, 164 mg VO^{2+} .

In certain embodiments, the compositions of the present invention include vanadyl sulfate hydrate as a vanadium source. In one such embodiment, the amount of elemental vanadium in the source of vanadium sulfate hydrate was determined by elemental analysis to be approximately 20% by weight, which corresponds to about five to six waters of hydration per molecule of vanadyl sulfate. For any embodiment using such a source of vanadyl sulfate hydrate, some of the common doses of vanadium and the resulting amount of vanadyl sulfate hydrate necessary to provide that amount of vanadium would be: 0.1 mg of vanadium, 0.5 mg of vanadyl sulfate hydrate; 20 mg of vanadium, 100 mg of vanadyl sulfate hydrate; 100 mg of vanadium, 500 mg of vanadyl sulfate hydrate.

In certain embodiments, the dose of vanadium may be modified if the supplement or composition contains a bioavailable source of chromium. For example, the dose of vanadium may be reduced by from about 10% to about 75%, or alternatively 25%, 33%, 55%, or 66%. The amount of reduction in the vanadium dose may depend, in part, on the dose of chromium provided for in any supplement of the present invention, as well as the source of the chromium and the means of administration.

For any of the components described herein, the dose may be varied as necessary, for example, to treat one or more specific conditions set forth herein, or for example, to reflect any differences in administration or the nature of the components employed in any particular composition, method or program of the present invention. For example, the dose of vanadium may be reduced as ingestion of the supplement results in improved blood glucose control. The

patient may need to monitor a number of indices, such as blood glucose levels or HbA1c levels, to determine the appropriate dosing.

In additional embodiments of present invention, the dose of vanadium is based on the weight of the intended recipient. Accordingly, in one embodiment of the present invention, the dose of vanadium is in the range of about 0.1 mg or less/kg of body weight up to about 10 mg or more/kg of body weight. In another embodiment of the present invention, the dose is at least about 0.3 mg/kg body weight. In still another embodiment of the present invention, the dose is in the range of about 0.2 mg/kg of body weight up to about 0.8 mg/kg of body weight.

Alternatively, dosages based on the subject's weight may be based on the amount of vanadyl required in any embodiment of the present invention. Accordingly, in one embodiment of the present invention, the dose of vanadyl is in the range of about 0.13 mg or less/kg of body weight up to about 13 mg or more/kg of body weight. In another embodiment of the present invention, the dose is at least about 0.42 mg/kg body weight. In still another embodiment of the present invention, the dose is in the range of about 0.26 mg/kg of body weight up to about 0.10 mg/kg of body weight.

In further embodiments of the present invention, the dose of vanadium may be determined based on the intended recipient's condition. For example, in one embodiment, the dose of vanadium may depend on the subject's HbA1c level. Accordingly, in this particular example, for a patient having an HbA1c level in the range of about 7 up to about 8, a dose of vanadium is in the range of about 0.05 mg or less/kg of body weight up to about 0.45 mg/kg; for a patient having an HbA1c level in the range of about 8 up to about 9, a dose of vanadium is in the range of about 0.15 mg/kg of body weight up to about 0.6 mg/kg of body weight, for a patient having an HbA1c level in the range of about 10 up to about 11, a dose of vanadium is in the range of about 0.3 mg/kg of body weight up to about 1.0 mg/kg of body weight, and for a patient having an HbA1c level in the range of at least about 11, a dose of vanadium in the range of about 0.35 mg/kg of body weight up to about 2.0 mg or more/kg of body weight. Dosing for a particular's subject condition may be based on any of the parameters known in the art or described herein useful for assessing the condition of any subject. For example, a number of parameters of blood serum, in addition to HbA1c levels, may be used to determine appropriate dosing. Other measurements of import of potential use for dosing purposes are described herein.

A number of vanadium containing compounds may be used in the present invention. For instance, vanadyl sulfate does not appear not to be associated with any apparent toxicity during

treatment periods of up to one year. In addition, it appears that vanadyl sulfate may be less toxic than vanadate forms of vanadium. Other vanadium compounds contemplated by the present invention include any of the following: vanadium pentoxide; vanadium trisulfate; vanadyl chloride; vanadyl glycinate; vanadyl gluconate; vanadyl citrate; vanadyl lactate; vanadyl tartrate; 5 vanadyl gluconate; vanadyl phosphate; sodium orthovanadate; vanadium chelidamate or arginate; and vanadyl complexes with monoprotric bidentate 2,4-diones. In addition to those vanadium complexes specifically set forth above, other organic, inorganic, salts and complexes of vanadium, including vanadyl complexes, known to those of skill in the art are contemplated by the present invention.

10 The different vanadium-containing metal complexes of the present invention may contain vanadium in any number of vanadium valencies. Vanadyl ion is VO^{2+} , which has vanadium in plus four oxidation state, is one form of vanadium that is preferred in supplements of the present invention.

15 3.1.3 Magnesium

Magnesium influences a broad diversity of functions in physiology and pathology. Magnesium is the second most abundant intracellular cation (positively charged element) in the body, predominately in muscle (skeletal and cardiac) and bone. It is required for over 300 enzymatic reactions.

20 For instance, magnesium is essential for maintaining the activity of the sodium potassium adenine triphosphate (Na-K-ATPase) pump. Magnesium deficiency results in depletion of intracellular potassium (the most abundant intracellular cation) and sodium accumulation. In cardiac muscle, this electrolyte abnormality may cause electrocardiographic changes and cardiac irritability, leading to myocardial infarction and potentially lethal arrhythmias.

25 The recommended daily allowance of magnesium for humans is 350 mg. Magnesium in mammals typically resides in three compartments: (1) bone; (2) intracellular bound form or an intracellular unbound form; and (3) in circulating bound and unbound forms. When the concentration of circulating magnesium in the bloodstream increases as a result of the dietary intake of magnesium, the magnesium is sequestered into one of the bound or intracellular forms. 30 Hypomagnesium is generally defined as a serum magnesium level concentration of less than 1.5 mEq/l.

The incidence of magnesium deficiency in Type 1 and Type 2 diabetes appears to be unclear. The diabetic patient may be at risk for developing magnesium depletion via inadequate dietary intake and gastrointestinal and renal losses, especially with poorly controlled blood glucose and resultant glucosuria. However, the diagnosing magnesium deficiency in the clinical setting remains extremely difficult because serum magnesium measures only 0.3% of the total body magnesium and is therefore difficult to determine.

Magnesium, as used in the present invention, appears to improve glucose metabolism and to arrest or reduce any diabetes associated risk factors. Many preparations of magnesium are available but they may differ in potency, bioavailability (absorption), tolerability, and cost.

Magnesium taken orally is absorbed primarily in the jejunum and ileum. Some magnesium salts, such as the oxide or the carbonate, although inexpensive, are not highly soluble in water, poorly absorbed and associated with gastrointestinal side effects, especially diarrhea. Other magnesium-containing complexes present better solubility, bioavailability, potency, tolerability, safety, and predictability in repleting intracellular and serum levels of magnesium.

Adjusting the dose as necessary for the particular magnesium complex employed, a number of magnesium containing complexes, or mixtures thereof, may be used in the subject preparations. Such molecules include: magnesium chloride; magnesium citrate; magnesium fumarate; magnesium succinate; magnesium orotate; magnesium aminodicarbonic acid fluoride, bromide and iodide; magnesium aspartate; magnesium stearate; magnesium glutamate; magnesium oxide; magnesium hydroxide; magnesium carbonate; magnesium hydrogen phosphate; magnesium glycerophosphate; magnesium trisilicate; magnesium hydroxide carbonate; magnesium acetate; magnesium citrate; magnesium gluconate; magnesium lactate; magnesium ascorbate; magnesium taurate; magnesium malate; and magnesium diglycinate.

It has been suggested that certain forms of magnesium are capable of increasing intracellular magnesium concentrations, whereas other magnesium supplements merely increase extra-cellular magnesium levels, which may result in less of a therapeutic effect or none at all. Two magnesium complexes that have been proposed to increase intracellular concentrations are magnesium orotate and magnesium aspartate.

Like many metal-containing complexes, the different magnesium compounds have different mechanisms of uptake in vivo. Additionally, upon administration, including ingestion, the transition metal complexes may undergo any number of reactions in vivo that affect the bioavailability and resulting therapeutic effect. By way of example, magnesium citrate is soluble

in gastric fluid and thus is readily available for passive absorption in the upper gastrointestinal tract. Magnesium and taurine may act to improve insulin sensitivity and to reduce vasoconstriction and atherogenesis, and stabilize platelets. Magnesium acetate, magnesium ascorbate and magnesium lactate are soluble in gastric fluid and share the upper gastrointestinal passive absorption potential of magnesium citrate. The ascorbate radical serves as a source of vitamin C by conversion to ascorbic acid upon exposure to hydrochloric acid in the gastric fluid, whereas the magnesium ion is converted to soluble magnesium chloride. The satisfactory water solubility of magnesium acetate, magnesium ascorbate, magnesium citrate and magnesium lactate provide for a diffusional gradient of magnesium in the upper small intestine where some passive absorption of magnesium occurs. Magnesium oxide is converted to magnesium chloride in the stomach, and offers the advantage of a high ionic magnesium content, since 60% by weight of the magnesium oxide molecule is elemental magnesium. Magnesium diglycinate represents a form of magnesium that is absorbed in part as an intact dipeptide in the proximal small intestine via a dipeptide transport pathway and therefore provides a third absorptive mechanism for magnesium. Magnesium stearate is useful as a lubricant when compressing the composition into tablets. The observations for these magnesium complexes is illustrative of the type of processes and chemical reactions that may occur for any of the transitional metal complexes described herein, including the chromium- and vanadium-containing complexes.

A variety of dosages, in amount of magnesium, are contemplated by the present invention. Unless expressly provided otherwise, the dose amounts referred to herein refer to the amount of magnesium in any particular form, such as any particular complex. The dose may range from about 5 mg or less to 1000 mg or more. Specific dosages include about 5 mg, 10 mg, 20 mg, 40 mg, 50 mg, 80 mg, 100 mg, 150 mg, 250 mg, 500 mg, 750 mg, 1000 mg, 1500 mg, and 2000 mg. A preferred dose is 46 mg of magnesium. Typically, these are daily dosages. Higher dosages, while they may be daily dosages, may be used as short term regimes (e.g. less than about one month) and may taper into dosages in the lower end of the ranges. In many such instances it will be advantageous to not to fall below about 40 to 100 mg per day of magnesium when tapering the dose. As for the chromium and vanadium components, the appropriate dose of magnesium may be based on the weight of the intended recipient. Alternatively, as discussed for other components, the appropriate dose of magnesium may be based on the condition of any subject, as assessed by a number of variables of import. Alternatively, the dosages may depend on the mode of administration. Alternatively, magnesium

does may vary with the identity and amounts of the other components in any supplement of the present invention. As for the other components of the subject compositions, appropriate dosages may depend on numerous factors, and may be readily determined by one of skill in the art.

5 3.1.4 *Aspirin (acetyl salicylic acid) and other anti-platelet agents*

Aspirin (e.g. acetyl salicylic acid) may be use to reduce the risk of either primary (high risk for cardiovascular disease) or secondary (cardiovascular disease). The health promoting benefits of aspirin derive in part from its antiplatelet effect. It appears to work, in part, by inhibiting cyclooxygenase, an enzyme necessary for the synthesis of thromboxane, a potent
10 stimulator of platelet aggregation, a condition known to be increased in diabetes and to be causative in the atherosclerotic process. In patients with diabetes and other glucose metabolism disorders, aspirin appears to correct this abnormal increase in platelet activity.

Platelet aggregation is implicated in thrombus formation, which involves interaction of aggregated platelets and activated coagulation factors with a damaged vascular wall. Platelets
15 are normally non-adherent, but upon damage to the endothelial lining of a vessel, the platelets adhere to exposed subendothelial collagen. The von Willebrand factor (vWF) is involved in this adhesion. Collagen and thrombin initiate platelet activation and activate phospholipase C, which hydrolyzes membrane phospholipids. Protein kinase C is thereby activated, and the calcium concentration of platelet cytosol increases. Arachidonic acid is liberated from membrane
20 phospholipids and is oxidized in part to prostaglandin H_2 (PGH_2) and TxA_2 . After platelet aggregation, fibrinogen is converted to fibrin to secure the hemostatic platelet plug. Platelet aggregation is mediated by the PGH_2 derivative prostacyclin, which is also a vasodilator. In the arachidonic acid cascade, aspirin acts as a cyclooxygenase inhibitor, blocking the conversion of arachidonic acid to the PGH_2 precursor prostaglandin G_2 (PGG_2). Because PGG_2 is a precursor
25 to both TxA_2 and prostacyclin, aspirin blocks both the aggregation inducing and aggregation inhibiting effects of these factors.

Like aspirin, naproxen, indomethacin, piroxicam and acetaminophen inhibit production of the pain-producing prostaglandins by cox-2, but they all, other than aspirin, substantially inhibit cox-1, which produces prostacyclin. Aspirin inhibits prostacyclin production the least (3-
30 4 hrs), and piroxicam the most (3-4 days). It is believed that that one aspirin taken every 3 days maximizes prostacyclin production and minimizes production of TxA_2 , which causes hypertension and has been implicated in development of vascular disease. Other non-

cylooxygenase inhibitors may be used for pain relief in addition to aspirin (e.g., Tramadol - Ultram), or inhibitors of cox-2 only (e.g., Meloxicam, and Sulindac (Clinoril)).

Because aspirin in doses above 80 mg per day may interfere with the synthesis of prostaglandins necessary to protect the gastric mucosa, gastrointestinal hemorrhage may result if aspirin is used above such a dose. Therefore, aspirin trials have used progressively smaller doses to avoid the risk of hemorrhage, and have found comparable suppression of thromboxane with doses as low as 10 mg per day and with equal or greater risk reduction for cardiovascular end point.

In certain embodiments, the present invention may use standardized willow bark as the source of aspirin. Standardized willow bark is a Chinese herb and is highly standardized source of aspirin. Alternatively, other, naturally occurring sources of acetyl salicylic acid may be used in the present invention. Typical dosage ranges of acetyl salicylic acid include less than 10 mg to 100 mg or more. Particular doses of aspirin include about 5 mg, 10 mg, 20 mg, 40 mg, 50 mg, 60 mg, 80 mg, 100 mg, 150 mg, 200 mg. Typically, these are daily dosages. Generally, although higher dosages are contemplated by the invention, they are less preferred because of potential gastric disturbances. In certain embodiments, it will be advantageous not to fall below about 40 to 80 mg per day when tolerable by a patient. As for the other components of the subject compositions, the appropriate dose of aspirin may depend on the mode of administration. As for the other components of the subject compositions, appropriate dosages may depend on numerous factors, and may be readily determined by one of skill in the art. Such factors include the weight of the intended recipient or the condition of the recipient.

3.1.5 Folic Acid (folate)

It is now well recognized that elevated blood homocysteine (a sulfhydryl-containing amino acid) levels are a cardiovascular risk factor. Homocysteine may injure arterial endothelial cells, may affect platelet-endothelial cell interaction, and may be thrombogenic. Such effects appear to accelerate the atherogenic process in diabetic patients. High homocysteine levels may be normalized by folic acid treatment, which thereby may reduce atherosclerotic events.

As with other the compounds of the present invention, the present invention may be practiced in the absence of folic acid, although in certain embodiments, the present invention will contain about 400 to about 600 mcg folic acid, or alternatively, about 400 mcg. Other possible doses include about 200 mcg or less, 300 mcg, 500 mcg, 600 mcg, and about 1000 mcg or more.

3.1.6 Vitamin E and other anti-oxidants

There is evidence that diabetes produces oxidative stress that may be related to the many of the complications that accompany diabetes, including cardiovascular problems. Therefore, compounds useful in reducing such stress may be valuable in the supplements of the present invention. Some possible candidates include the following:

a. Vitamin E

Vitamin E (free 2R, 4'R, 8'R-alpha-tocopherol) is the most widely studied of the antioxidant vitamins. The interest in vitamin E as an antioxidant is based on the many demonstrations in humans that giving vitamin E as a supplement decreases the oxidation of low density lipoprotein (LDL) ex vivo, an event critical in the atherogenic process.

It is believed that Vitamin E supplementation reduces significantly atherosclerosis in primates, including humans. This observation assumes greater importance in those with diabetes, in view of the fact that as many as 60% of newly diagnosed diabetic patients already have clinically obvious cardiovascular disease. A number of studies confirm such observation/ A significantly lower risk of coronary artery disease was observed in a four year, prospective, observational study in healthy middle-aged men who had higher intakes of dietary vitamin E as compared to those consuming small amounts. In another prospective, epidemiological study, middle-aged women free of cardiovascular disease at baseline were found to have a highly significant reduced risk of coronary artery disease if they had been on vitamin E supplements for at least two years during the eight year study. In a more recent and similar seven year prospective study of postmenopausal women without cardiovascular disease, dietary vitamin E consumption, but not vitamin A or C, was inversely associated with the risk of death from coronary artery disease.

The Cambridge Heart Antioxidant Study ("CHAOS") investigated vitamin E supplementation in patients with coronary artery disease. CHAOS was a nearly three year prospective, secondary interventional trial of 2002 men and women, 10% of whom had diabetes, using vitamin E (free 2R, 4'R, 8'R-alpha-tocopherol), 400 or 800 I.U. daily, in a randomized, placebo-controlled, double-blinded design. Either dose of vitamin E was associated with a dramatic and significant reduction of non-fatal myocardial infarction. The benefit of treatment

with vitamin E was apparent after two hundred days, and the patients with diabetes also enjoyed the marked reduction in the risk of non-fatal heart disease.

Another benefit of vitamin E supplementation is believed to be the favorable effect it has on insulin sensitivity, glucose metabolism, and lipid levels in both healthy subjects and patients with Type 2 diabetes. Conversely, in a prospective study of almost one thousand non diabetic, middle-aged men, low concentration of plasma vitamin E at baseline was found to be an independent and powerful predictor for the development of Type 2 diabetes during the four year study. A low level of vitamin E was associated with a greater than five-fold risk of developing diabetes in the ensuing four years. In addition, vitamin E may restore reduced prostacyclin synthesis, thereby possibly treating neuropathy.

Vitamin E was well tolerated in the studies where it was given as a supplement, and in the CHAOS study, there was no difference between the alpha-tocopherol treatment (400 or 800 I.U.) or placebo groups for side effects. Because of the unusually high incidence of clinical heart disease in newly diagnosed diabetic patients, and the favorable effect vitamin E has on the metabolic abnormalities of Type 2 diabetes, the present invention may contain vitamin E. Dosages may range up to 1200 I.U. or more, especially 400-800 I.U., and particularly 400 I.U.

In addition to using alpha-tocopherol and its analogs and esters thereof, e.g., alpha-tocopherol acid succinate and alpha-tocopherol acetate, other equivalents of tocopherols may be used in the subject preparations, such as tocotrienols and their esters, and tocopheryl nicotinate. Gamma tocopherol are believed to trap mutagenic electrophiles such as NOx. Alpha-tocopherol acid succinate may be useful for preparing supplements in tablet form.

b. Alpha-lipoic acid

Alpha-lipoic acid is an antioxidant and is an essential coenzyme in the utilization of sugar (glucose) for energy production. Alpha-lipoic acid also assists the body recycle and renew other antioxidants, e.g. vitamins C and E, Co-Q10 and glutathione, and neutralizes both oxygen and nitrogen free radicals, which are believed to play major causal roles in cardiovascular diseases. It has been suggested that alpha-lipoic acid may increase intracellular glutathione levels. More recently, administration of alpha-lipoic acid to diabetic patients with neuropathy appeared to reduce significantly associated symptoms. In addition, DL-lipoic acid has been recommended for treatment of a metabolic aberration of pyruvate dehydrogenase, which is

symptomatic of diabetes. Also, alpha-lipoic acid has been used to treat circulatory problems resulting from diabetes.

In certain embodiments, the present invention will contain about 10 mg or less to about 600 mg or more alpha-lipoic acid, with the most preferred dose of 50 mg. Other possible
5 dosages include 10 mg or less, 25 mg, 75 mg, 100 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 500 mg, 600 mg, and 750 mg or more. If a patient presents with neuropathy, an increased dose of alpha-lipoic acid may be appropriate.

3.1.7 Vitamin A

10 The present invention contemplates formulations containing vitamin A, including retinoids, β -carotene, α -carotene, cryptoxanthine, and other equivalents. Possible dosages of Vitamin A or its equivalents include up to 5000 I.U. or more.

15 These components may be combined in certain embodiments with other vitamin and mineral supplements. These additional ingredients may be taken simultaneously. Other vitamins and minerals are important in the metabolism of glucose and the maintenance of good health and may be ingested from food or included in a supplement. Some of these other vitamins and minerals include calcium, copper, and zinc.

It should be recognized that the amounts of these vitamins and minerals may vary widely
20 within the scope of the present invention.

3.2 Dosage and Assays of Supplements, or Components Thereof

The dosage of any supplement, or any component thereof, of the present invention will vary depending on the symptoms, age and body weight of the patient, the nature and severity of
25 the disorder to be treated or prevented, the route of administration, and the form of the supplement. Possible dosage ranges and particular dosages have been presented above in discussing different components that may be present in any supplement or composition of the present invention. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for supplements, or components thereof, may be readily determined by
30 techniques known to those of skill in the art or as taught herein.

An effective dose or amount, and any possible affects on the timing of administration of the formulation, may need to be identified for any particular supplement, or component thereof,

of the present invention. This may be accomplished by routine experiment as described herein, using one or more groups of animals (preferably at least 5 animals per group), or in human trials if appropriate. The effectiveness of any supplement and method of treatment or prevention may be assessed by administering the supplement and assessing the effect of the administration by measuring one or more indices associated with glucose metabolism, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment.

The precise time of administration and/or amount of any particular supplement that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, etc. The guidelines presented herein may be used to optimize the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

While the subject is being treated, glucose metabolism may be monitored by measuring one or more of the relevant indices at predetermined times during a 24-hour period. Treatment, including supplement, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters, the first such reevaluation typically occurring at the end of four weeks from the onset of therapy, and subsequent reevaluations occurring every four to eight weeks during therapy and then every three months thereafter. Therapy may continue for several months or even years, with a minimum of three months being a typical length of therapy for humans.

Adjustments to the amount(s) of agent(s) or supplement(s) administered and possibly to the time of administration may be made based on these reevaluations. For example, if after four weeks of treatment one of the metabolic indices has not improved but at least one other has, the dose of different components of the formulation might be increased by, for example, one-third. For example, if blood glucose levels have not decreased sufficiently after a period of treatment by a formulation of the present invention, then the dosages of chromium and vanadium-containing complexes may be increased, or alternatively other complexes may be used, whereas the dose of aspirin would not necessarily need to be adjusted.

Treatment may be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum therapeutic effect is attained.

The combined use of several components in any supplement may reduce the required dosage for any individual component because the onset and duration of effect of the different components may be complimentary. In such combined therapy, the different components may be delivered together or separately, and simultaneously or at different times within the day. Often, the different components may be administered substantially simultaneously, or alternatively as a composition or formulation containing both components. For example, it is known that vitamin C may regenerate and spare vitamin E, so any formulation having both of these compounds may provide complimentary protection against oxidative stress.

For assaying different supplements, or components thereof, and different treatment regimens, a variety of indices may need to be measured. For example, in an oral glucose tolerance test, a patient's physiological response to a glucose load or challenge is evaluated. After ingesting the glucose, the patient's physiological response to the glucose challenge is evaluated. Generally, this is accomplished by determining the patient's blood glucose levels (the concentration of glucose in the patient's plasma, serum, or whole blood) at several predetermined points in time. Another related method is the hyperinsulinemic-euglycemic clamp.

Blood glucose measurements may be made by any number of methods. The timing of any blood glucose test may be material, and the present invention contemplates determining the fasting blood glucose level and especially the post-prandial blood glucose level. In general, the desirable fasting glucose level (or pre-prandial) is 80 to 120 mg/dL, and a non-diabetic has a pre-prandial glucose level of less than 110 mg/dl. The desirable post-prandial level (or bedtime glucose level) is 100 to 140 mg/dL, and a non-diabetic has a bedtime glucose level of less than 120 mg/dl. Under the American Diabetes Clinical Practice Recommendations, additional action is recommended if the fasting blood glucose level is greater than 140 mg/dl or the post-prandial glucose level is greater than 160 mg/dl. For older patients, or those with related complications, different treatment goals may be appropriate.

Some measurement methods for glucose employ invasive techniques, which require taking a blood sample from the subject. Many invasive glucose sensors are based on electrochemical methods such as the electroenzymatic method. Three enzymes are often used: glucose oxidase, hexokinase and glucose dehydrogenase. For example, blood glucose is

oxidized by glucose-oxidase to produce gluconic acid and hydrogen peroxide. Glucose concentrations may be determined by measuring oxygen consumed or hydrogen peroxide produced (amperometric method), or by measuring gluconic acid produced (potentiometric method).

5 Alternatively, it may be possible to determine blood glucose levels by using non-invasive methods. Non-invasive technologies that have been used or proposed for measuring glucose levels in tissue include: near-IR transmission and reflectance, Near-IR Kromoscopy, spatially resolved diffuse reflectance, polarimetry measurements, Raman measurements, and PA measurements. In another example, it is possible to monitor a patient's blood glucose levels and
10 insulin levels by monitoring ECG changes upon glucose uptake. This method does not work for Type 1 diabetic patients, however, because they lack the necessary pancreatic insulin response. In another method, blood glucose levels may be measured by irradiating blood vessels in the retina of the eye. Finally, other spectroscopic methods have been proposed and are known to those of skill in the art.

15 Another clinical index for glucose metabolism is glycosylated hemoglobin A. Human adult hemoglobin (Hb) typically consists of HbA, HbA2, and HbF. These forms of hemoglobin differ by virtue of their primary structure (i.e., amino acid sequence). Normally, HbA constitutes about 97% of the total hemoglobin present, HbA2 constitutes about 2.5% of the total, and HbF, also known as fetal hemoglobin, only about 0.5%.

20 Chromatographic analysis of HbA has shown that it contains a number of minor hemoglobin species. These minor species have been designated HbA1a, HbA1b, and HbA1c. These species are referred to as glycosylated hemoglobins or glycohemoglobins, and are formed by condensation of the amino group of the hemoglobin with a keto moiety of a sugar. For HbA1c, the sugar is glucose, and the glycosylated hemoglobin is formed by the condensation of
25 the N-terminal valine amino acid of each β -chain of hemoglobin with glucose to form an unstable Schiff base or aldimine (also known as pre-A1c), which then undergoes an Amadori rearrangement to form a stable ketoamine. Methods have been developed to distinguish between the stable and labile forms of HbA1c so as to provide more accurate measurements of the stable HbA1c.

30 The formation of glycosylated hemoglobins is non-enzymatic and occurs over the lifespan of the red cell, which is about 120 days under normal conditions. The amount of HbA1c is proportional to the concentration of glucose in the blood, and is therefore related to time-

averaged glucose concentration over the period prior to the measurement, which is approximately two to three months. HbA1c values may be used to assess diabetic control, in which short-term fluctuations in plasma glucose levels do not affect the measurement. In general, the desirable HbA1c level is less than 7%, and less than 6% in a non-diabetic. Under the American Diabetes
5 Clinical Practice Recommendations, additional action is recommended if a patient's HbA1c level exceeds 8%. VHA guidelines recommend measuring HbA1c levels at least once annually.

Measurement of glycosylated hemoglobins may augment other traditional methods of assessing control of glucose metabolism. For example, measurement of glycosylated hemoglobins may be used when urine glucose records are inadequate, when blood glucose levels
10 vary markedly throughout the day or from day to day, and for a new patient with known or suspected diabetes in whom there is no previous record of blood glucose concentration. Control of HbA1c levels by the present invention may reduce such AGE-related products.

There are a number of currently available methods for determining levels of glycosylated hemoglobins, including ion exchange chromatography, high-performance liquid
15 chromatography, affinity chromatography, colorimetry, radioimmunoassay, electrophoresis, and isoelectric focusing. Ion exchange chromatography may be conducted using resins containing weakly acidic cation exchanges or negatively charged carboxymethylcellulose resin. High performance liquid chromatography provides a reliable reference method.

Affinity chromatography may be used to separate non-glycosylated hemoglobin from
20 glycosylated hemoglobin. A suitable affinity column is prepared having immobilized m-aminophenylboronic acid. The boronic acid reacts with the cis-diol groups of glucose bound to hemoglobin to form a reversible 5-membered ring complex, thus selectively binding the glycosylated hemoglobin to the affinity column. Sorbitol disassociates glycosylated hemoglobin from the column. For example, glycosylated hemoglobin may be measured by a modification of
25 the method of Clegg and Schroeder.

A calorimetric method has been devised based on the observation that HbA1c, when subject to mild acid hydrolysis, releases 5-hydroxymethylfurfural (5-HMF). Another spectrophotometric method involves the reaction of inositol hexaphosphate (phytic acid) with hemoglobin. Absorbance increases at 633 nm and decreases at 560 nm. upon phytic acid binding
30 to the N-terminal amino groups of the β -chains. This change only occurs for Hb A that is unglycosylated, so the change in absorbance induced by phytic acid is thus inversely proportional to the fraction of glycosylated hemoglobin.

Antibody directed against HbA1c may be prepared and used as the basis for a radioimmunoassay. Isoelectric focusing has also been used as a method of quantitating HbA1c. In another method, capillary electrophoresis may be used, usually in conjunction with an antibody directed against HbA1c.

5 Kits for measuring glycosylated hemoglobin are known in the art, and contemplated by the present invention.

Fasting glucose levels may be measured by finger stick glucometer readings. Samples of apolipoproteins may be analyzed on a protein analyzer using proper standardization techniques. Other indices may be measured by techniques known to those of skill in the art.

10 Animal-based studies may be conducted on different supplements, or components thereof, of the present invention as necessary to determine combinations of the different components that produce the greatest therapeutic effect. For example, in rats the diabetic state may be induced by injecting streptozotocin (STZ) at an appropriate dose, for example 60 mg/kg dissolved in 0.9% NaCl IC via the tail vein upon anaesthetization. The diabetic state may be
15 confirmed at a later time, whereupon assaying of different supplements may begin thereafter. Alternatively, insulin resistant spontaneously hypertensive rats (SHR) made be used, with the genetic control being the Wistar Kyoto (WKY) strain. Alternatively, the Zucker diabetic fatty rat (ZDF) a model of spontaneous NIDDM, may be used, with the Zucker lean control (ZLC) rats as controls. In addition, transgenic mouse models may be useful in the present invention.

20 Alternatively, the db/db mouse, a genetically obese and diabetic strain of mouse, may be used in animal studies. The db/db mouse develops hyperglycemia and hyperinsulinemia concomitant with its development of obesity and thus serves as a model of obese Type 2 diabetes. The db/db mice may purchased from, for example, the Jackson Laboratories (Bar Harbor, Me.). In an exemplary embodiment, for treatment of mice with a regimen including a
25 formulation of the present invention or control, sub-orbital sinus blood samples may be taken before and at some time after dosing of each animal.

Toxicity and therapeutic efficacy of supplements, or components thereof, may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose
30 therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it may be expressed as the ratio LD₅₀/ED₅₀. Compositions that exhibit large therapeutic indices are preferred. Although supplements that exhibit toxic side

effects may be used, care should be taken to design a delivery system that targets the component(s) of any supplement responsible for any toxic effects to the desired site in order to reduce side effects.

The data obtained from the cell culture assays and animal studies may be used in formulating a range of dosage for use in humans. The dosage of any supplement, or alternatively of any components therein, lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any supplement or components thereof of the present invention, the therapeutically effective dose may be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information may be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

3.5 Formulations of Supplements, Compositions, and Components or Ingredients Thereof

The compositions and supplements of the present invention may be administered in various forms, depending on the disorder or condition to be treated and the age, condition and body weight of the patient, as is well known in the art. For any of the modalities presented herein, different components of any subject supplement may be administered by different methods as necessary for effective delivery of the component, or as otherwise necessary for convenience. For example, where the formulation is to be administered orally, it may be formulated as tablets, capsules, granules, powders or syrups. Alternatively, formulations of the present invention may be administered parenterally as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations, or suppositories. For application by the ophthalmic mucous membrane route, they may be formulated as eyedrops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the active ingredient may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

In formulations of the subject supplements and compositions, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents,

release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the supplements.

Formulations useful in the methods of the present invention include those suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of supplement or components thereof which may be combined with a carrier material to produce a single dosage form will vary depending upon the subject being treated, and the particular mode of administration. The amount of active ingredient which may be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect. Generally, out of one hundred per cent, this amount may range from about 1 per cent to about ninety-nine percent of active ingredient, particularly from about 5 per cent to about 70 per cent, especially from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a supplement or components thereof with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a supplement or components thereof with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a supplement or components thereof as an active ingredient. A supplement or components thereof may also be administered as a bolus, electuary, or paste.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the supplement or components thereof is mixed with one or more pharmaceutically-acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain

silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the supplement or components thereof moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

Tablets and other solid dosage forms may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which may be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which may be used include polymeric substances and waxes. The active ingredient may also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the

supplement or component, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ,
5 olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

10 Suspensions, in addition to the supplement or components thereof, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Pharmaceutical compositions of this invention suitable for parenteral administration
15 comprise one or more components of a supplement in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or
20 suspending or thickening agents.

Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity may be
25 maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These formulations may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben,
30 chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition,

prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a component of a supplement, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This
5 may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

10 Injectable depot forms are made by forming microencapsule matrices of components of a supplement in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of component to polymer, and the nature of the particular polymer employed, the rate of component release may be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by
15 entrapping the component in liposomes or microemulsions which are compatible with body tissue.

Exemplification

The present invention now being generally described, it may be more readily understood
20 by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

Example One

25 The different supplements of the present invention are presently referred to as GLUCOSTAT™. One example of an embodiment of the present invention constitutes a packet containing 4 tablets:

Three tablets contain chromium picolinate, vanadyl sulfate hydrate, vitamin E natural, standardized willow bark (aspirin), folic acid, alpha-lipoic acid and a multivitamin/mineral
30 formula; and,

One tablet contains magnesium chloride.

Specifically, each dose of this embodiment in this Example One contains the following (component, and amount): Chromium (as chromium picolinate) 333 mcg, 1000 mcg; Vanadyl sulfate hydrate, 100 mg; Vitamin E natural (free 2R, 4'R 8'R-alpha-tocopherol), 400 I.U.; Magnesium chloride hexahydrate 384 mg; Folic acid (folate), 400 mcg; Vitamin A 5000 I.U.; Vitamin C, 60 mg; Vitamin K 34.00 mcg; Thiamine, 3.00 mg; Riboflavin, 3.60 mg; Niacinamide, 20.10 mg; Vitamin B-6, 23.10 mg; Vitamin B-12, 48.00 mcg; Biotin, 300 mcg; Pantothenic acid, 10.00 mg; Calcium, 150 mg; Phosphorus, 115.00 mg; Iodine, 150.00 mcg; Zinc, 15.00 mg; Selenium, 60.00 mcg; Copper, 2.00 mg; Manganese, 11.00 Mg; Molybdenum, 75.00 mcg. This embodiment also contains 160 mg standardized willow bark (aspirin 20 mg), a Chinese herb and a source of aspirin. In the examples described herein, chromium picolinate was obtained from Nutrition 21 or AMBI Inc., and chromium polynicotinate was obtained from InterHealth. The vanadium sulfate hydrate in this Example One was determined to contain about 20% elemental vanadium by weight, which corresponds to about five to six waters of hydration for every molecule of vanadyl sulfate.

Over twenty patients with both Type 1 and Type 2 diabetes using the present embodiment have reported a significant reduction in blood glucose levels, ranging from 30 mg/dl to as much as 115 mg/dl. These reductions have been noted within as little as two weeks from initiating the present system to as long as a seven to twelve week period. Patients have usually noted a 19 to 47% drop in their baseline blood sugars following treatment with this embodiment, with the average response being an approximate 30% reduction. Likewise, the HbA1c levels have dropped on average a point after 3 months of use with this embodiment, with one patient reporting an 8 point drop from the pre-system HbA1c. Generally, most patients report a 15% reduction in baseline HbA1c after approximately three months of treatment.

In addition to improved glucose metabolism, serum cholesterol have been reported to be reduced in patients ingesting this embodiment. Absolute reductions in serum cholesterol following the program have ranged from 20 to 67 mg/dl, representing an 11 to 27% decrease from baseline levels.

Patients ingesting this subject composition have also reported a drop in blood pressure levels. The systolic drop in blood pressure has ranged from 20-30 mmHg, with a 10-22 mmHg drop in diastolic measurements. Overall, there has been an 8-12% drop in blood pressure.

Many of the subjects have noted significant weight loss on this program. The absolute weight loss has ranged from 7-16 pounds, with an 8% loss of total body weight.

Example Two

In another example, a group of Type 2 diabetic individuals presenting with elevated HbA1c levels were placed on a program using another embodiment of the present invention. The study was conducted as an open-label study at two different medical centers in the United States. The patients were on the program for three months, and were directed not to change their dietary habits or lifestyle, including exercise patterns. The patients were not taking any other medication for their diabetic condition.

For this Example Two, one daily dose of this embodiment contained (component and amount):

Vitamin A, 5000 IU; Vitamin C (Ascorbic Acid), 60 mg; Vitamin D-3, 400 IU; Vitamin E, 400 IU; Thiamine (as Thiamine Mononitrate), 3 mg; Riboflavin, 3.6 mg; Niacinamide, 20.1 mg; Vitamin B-6 (as Pyridoxine HCl), 23.1 mg; Folic Acid, 400 mcg; Vitamin B-12, 48 mcg; Biotin, 300 mcg; Pantothenic Acid (as Calcium Pantothenate), 10 mg; Calcium (from Calcium Carbonate/Phosphate), 150 mg; Phosphorous (from Calcium Phosphate), 115 mg; Iodine (from Sea Kelp), 150 mg; Magnesium (elemental Magnesium from 307 mg Magnesium Complex of citrate/fumuate/malate/gluturate/succinate/chloride), 46 mg; Zinc, 15 mg; Selenium (from Selenium Krebs), 60 mcg; Manganese (from Manganese Sulfate), 11 mg; Chromium (from 3264 mcg Chromium Picolinate/Polynicotinate Complex (50%/50%)), 333 mcg; Vanadyl Sulfate hydrate, 100 mg; Willow (bark) (standardized willow/willow bark complex) (aspirin 20 mg), 160 mg. The same source of vanadium sulfate hydrate was used in this Example Two as was used in Example One.

Table A: Results of Treatment Program:

Patient Number	HbA1c Level <u>Before</u> Program	HbA1c Level <u>After</u> Program	Change in HbA1c Level
1	8.6	6.6	2.0
2	12.7	9.6	3.1
3	8.1	5.7	2.4
4	7.6	5.7	1.9
5	8.3	7.6	0.7
6	9.3	7.7	1.6
7	10.4	7.3	3.1
8	11.9	8.9	3.0
9	8.8	6.0	2.8
10	8.3	7.8	0.5
Average Value for Ten Patients	9.40	7.29	2.11

The patients report, on average, as 2.11 drop in HbA1c levels.

5 **References**

All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

10

Patents and patent applications

U.S. Patent No. Re. 33,988

U.S. Patent No. 4,255,385

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U.S. Patent No. 4,959,222

U.S. Patent No. 4,966,588

U.S. Patent No. 5,045,316

U.S. Patent No. 5,087,624

U.S. Patent No. 5,212,154

U.S. Patent No. 5,292,663

U.S. Patent No. 5,431,793

5 U.S. Patent No. 5,532,269

U.S. Patent No. 5,599,835

U.S. Patent No. 5,665,385

U.S. Patent No. 5,710,630

U.S. Patent No. 5,741,211

10 U.S. Patent No. 5,789,401

U.S. Patent No. 5,820,557

U.S. Patent No. 5,824,840

Publications and other references

15

Abbott et al, JAMA 260:3456-60 (1988)

Anderson, J. Am. College Nutrition 17:548-55 (1998).

American Diabetes Association, Diabetes Care 20 (Suppl. 1):S14-17 (1997)

Arsenian et al., Prog. Cardiovasc.Dis. 35:271-310 (1993)

20 Baker et al., Diabetes Educ. 18:420-27 (1992)

Barnard et al., Diabetes Care 17:1469-72 (1994)

Bierman et al., Arterioscler. Thromb. 12:647-56 (1992)

Bisse et al., J. Chromotography 434 95-110 (1988)

Busse et al., Drug Res. 42:829-31 (1992).

25 Caballero, Nutr. Rev. 51:339-340 (1993)

Cam et al., Diabetologia 36:218-24 (1993)

Chowdhury et al., Postgrad Med. J. 74:480-81 (1998)

Christen et al., PNAS USA 94:3217-22 (1997).

Clarke et al., N. Eng. J. Med. 325:1137-41 (1991)

30 Classen et al., 6 Recent Advances in Studies on Cardiac Structure and Metabolism 111-18 (University Park Press 1975)

Classen et al., Magnesium 3:257-64 (1984)

- Clegg et al., J. Lab Clin. Med. 102:577-89 (1983)
- Cohen et al., JAMA 249:2808-10 (1983)
- Colwell et al., Metabolism 26:279-85 (1977)
- Dai et al., Pharmacol. & Toxicol. 74:101-09 (1994)
- 5 Davi et al., Arterioscler. Thromb. 13:1346-49 (1993)
- Davis et al., Curr. Ther. Res. 36:341-46 (1984)
- Defronzo et al., Diabetes Care 14:173-94 (1991)
- Dieber-Rotheneder et al., J. Lipid Res. 32:1325-32 (1991)
- Drvota et al., Adv. Prost. Throm. Leuk. Res. 21A:153-56 (1990)
- 10 Entmacher et al., Diabetes 13:373-77 (1964)
- Ewald et al., Acta Paediatr. Scand. 72:367-71 (1983)
- Franz et al., Diabetes Care 17:490-518 (1994)
- Freund et al., JAMA 241:496-98 (1979)
- Goldstein, et al., C.R.C. Critical Reviews in Clinical Laboratory Sciences 21:187-228
- 15 Goyder et al., BMJ 317:1644-46 (1998)
- Guthrie et al., Diabetes Care 15:1494-98
- Guyton, Textbook of Medical Physiology 855-67 (8th ed. 1991)
- Haffner et al., Diabetes 41:715-722 (1992);
- Haffner et al., JAMA 263:1893-98 (1990);
- 20 Harris, in Diabetes in America (2d ed., NIH 1995)
- Harris et al., Diabetes Care 15:815-19 (1992)
- Heath et al., Diabetologia 7:308-15 (1971)
- International Textbook of Diabetes Mellitus (Alberti et al. eds, John Wiley:1992)
- Jarrett et al., Diabetologia 22:79-84 (1982)
- 25 Javitt et al., in Diabetes in America (2d ed., NIH 1995)
- Jeejeebhoy et al., Am. J. Clin. Nutr. 30:531-38 (1977)
- Julkunen-Tiito et al., Planta Medica 55:55 (1989)
- Kalgutkar et al., Science 280:1268-70 (1998)
- Kannel, Am. Heart J. 110:1100-07 (1985)
- 30 Kaplan, Arch. Intern. Med. 149:1514-20 (1989)
- Khalil, Clinical Chemistry 45:165-77 (1999)
- Klein et al., Ophthalmology 91:1-9 (1984)

- Kruse-Jarres et al., Clin. Chem. Clin. Biochem. 26:201-08 (1988)
- Kunisaki et al., Metabolism 41:613-21 (1992)
- Kushi et al., N. Engl. J. Med. 334:1156-62 (1996)
- Kuusisto et al., Diabetes 43:960-67 (1994)
- 5 Kwaan et al., J. Lab. Clin. Med. 20:235-46 (1972)
- Lancet 336:827-30 (1990)
- Lancet 338:1345-49 (1991).
- Lardinois, Geriatrics 53:22-39 (1998)
- Levine et al., Diabetologia 21:131-34 (1981)
- 10 Lee et al., Ann. Intern. Med. 120:184-90 (1994)
- Lipid Research Clinic's Program, JAMA 251:351-74 (1984)
- Lippard et al., Principles of Bioinorganic Chemistry (1994)
- Malabu et al., Diabetes 43:9-15 (1994)
- Margolis et al., Am. J. Cardiol. 31:1-7 (1973)
- 15 Marier, Can. Biol. 37:115-25 (1978)
- Mertz, Nutr. Rev. 33:129-35 (1975)
- McNair et al., Eur. J. Clin. Invest. 12:81-85 (1982)
- McPhillips et al., Am. J. Epidemiology 131:443-53 (1990)
- Molten et al., Electrophoresis 15:22-30 (1994)
- 20 Mooradian et al., Diabetes Care 17:464-79 (1994).
- Orchard et al., Circulation 88:819-28 (1993)
- Paolisso et al., Am. J. Hypertens. 10:346-55 (1997)
- Paolisso et al., Am. J. Clin. Nutr. 57:650-56 (1993)
- Paolisso et al., Diabetes Care 16:1433-37 (1993)
- 25 Preuss et al., Clinical Nephology, 47:325-30 (1997)
- Reaven, Diabetes 37:1595-607 (1988)
- Reinhart, Arch Intern. Med. 148:2415-20 (1988)
- Resnick et al., Am. J. Med. 93 (Suppl. 2A):2A11S-2A20S (1992)
- Rimm et al., N. Engl. J. Med. 328:1450-56 (1993)
- 30 Rubin et al., J. Clin. Endocrinol. Metab. 78:809A-09F (1994)
- Rude, Am. J. Cardiol. 63:31G-34G (1989)
- Ryzen Am. Heart J. 111:475-80 (1986).

- Saad et al., Lancet I:1356-59 (1989)
- Sagel et al., Ann. Intern. Med. 83:733-38 (1975)
- Sakuri et al., Biochem. Biophys Res. Commun. 96:293-98 (1980)
- Salonen et al., BMJ 311:1124-27 (1995)
- 5 Seelig et al., Am. J. Cardiol. 63:4G-21G (1989)
- Sjogren et al., Acta Med. Scand. 224:461-65 (1988)
- Stamler et al., Diabetes Care 16:434-44 (1993)
- Stampfer et al., N. Engl. J. Med. 328:1444-49 (1993)
- Steinberg et al., N. Engl. J. Med. 320:915-20 (1989)
- 10 Steinberg, Circulation 85:2337-44 (1992)
- Stephens et al., Lancet 347:781-86 (1996)
- Tomlinson, Diabetes & Metabolism (Paris) 24:79-83 (1998)
- Tosiello et al., Arch Intern. Med. 156:1143-48 (1996)
- Tsui et al., Endocrinologist 5:263-71 (1995)
- 15 USRDS 1994 Annual Data Report (NIH 1994)
- Vane, Nature 231:232 (1971)
- Verlangieri et al., J. Am. Coll. Nutr. 11:131-38 (1992)
- Vital and Health Statistics Series 10, no. 190 (1994)
- Whang et al., Am. J. Med. 82 (Suppl. 3A):24-29 (1987)
- 20 Zeigler et al., Diabetes Care 20:369-73 (1997)

Equivalents

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications may be made thereto without requiring more than

25 routine experimentation or departing from the spirit or scope of the appended claims.

What is claimed is:

1. A program for treating or preventing glucose metabolism disorders in a subject, comprising:
 - 5 a. determining a first HbA1c level and a first body weight of a subject presenting a glucose metabolism disorder;
 - b. providing, in a pharmaceutically acceptable excipient, a first composition comprising:
 - 10 i. a first bioavailable source of chromium in an amount determined by said first HbA1c level: for said subject having said first HbA1c level in the range of about 7 up to about 8%, said amount of chromium from about 0.003 mg Cr or less/kg of said first body weight up to about 0.009 mg Cr/kg of said first body weight; for said subject having said first HbA1c level in the range of about 8 up to about 9%, said amount of chromium
15 from about 0.005 mg Cr/kg of said first body weight up to about 0.01 mg Cr/kg of said first body weight; for said subject having said first HbA1c level in the range of about 10 up to about 11%, said amount of chromium from about 0.006 mg Cr/kg of said first body weight up to about 0.015 mg Cr/kg of said first body weight; or for said subject having said first HbA1c
20 level in the range of at least about 11%, said amount of chromium from about 0.007 mg Cr/kg of said first body weight up to about 0.04 mg Cr or more/kg of said first body weight; and,
 - ii. a first bioavailable source of vanadium in an amount determined by said first HbA1c level: for said subject having said first HbA1c level in the
25 range of about 7 up to about 8%, said amount of vanadium from about 0.05 mg V or less/kg of said first body weight up to about 0.4 mg V/kg of said first body weight; for said subject having said first HbA1c level in the range of about 8 up to about 9%, said amount of vanadium from about 0.15 mg V/kg of said first body weight up to about 0.5 mg V/kg of said
30 first body weight, for said subject having said first HbA1c level in the range of about 10 up to about 11%, said amount of vanadium from about 0.3 mg V/kg of said first body weight up to about 1.0 mg V/kg of said first

body weight, or for said subject having said first HbA1c level in the range of at least about 11%, said amount of vanadium from about 0.35 mg V/kg of said first body weight up to about 2.0 mg V or more/kg of said first body weight;

- 5 c. directing said subject to ingest said first composition on a first regular basis for a first period;
- d. determining a second HbA1c level and a second body weight for said subject at about the end of said first period;
- e. comparing said second HbA1c level to said first HbA1c level to determine any
10 improvement in glucose metabolism by said subject during said first period.
2. The program of claim 1, wherein said glucose metabolism disorder comprises one of the following: Type 1 diabetes, Type 2 diabetes, MODY or IGT.
- 15 3. The program of claim 1, wherein said subject is pre-diabetic.
4. The program of claim 1, wherein said program improves one or more of the following conditions: insulin resistance, beta cell attrition, hyperinsulinemia, hyperglycemia, elevated blood glucose levels, coronary artery disease or arteriosclerosis.
- 20 5. The program of claim 1, wherein said program modulates one or more of the following conditions: blood pressure, hyperlipoproteinemia, hypertriglyceridemia, serum cholesterol level, HDL level, LDL level, dyslipidemia, atherosclerosis or CHD.
- 25 6. The program of claim 1, wherein said first bioavailable source of chromium comprises chromium picolinate or chromium polynicotinate.
7. The program of claim 6, wherein said first bioavailable source of chromium comprises chromium polynicotinate.
- 30 8. The program of claim 1, wherein said first bioavailable source of vanadium comprises vanadyl and a counter-ion.

9. The program of claim 8, wherein said counter-ion is sulfate.
10. The program of claim 1, wherein said first bioavailable source of chromium comprises
5 either chromium picolinate or chromium polynicotinate, and said first bioavailable source
of vanadium comprises vanadyl and a counter-ion.
11. The program of claim 1, wherein said first bioavailable source of chromium is chromium
polynicotinate, and said first bioavailable source of vanadium is vanadyl sulfate.
10
12. The program of claim 1, wherein said first composition further comprises a
therapeutically effective amount of one or more of following: aspirin, a bioavailable
source of magnesium, folic acid, vitamin E or vitamin A.
- 15 13. The program of claim 1, wherein said first composition further comprises a
therapeutically effective amount of aspirin.
14. The program of claim 1, wherein said first composition further comprises a
therapeutically effective amount of alpha-lipoic acid.
20
15. The program of claim 1, wherein said first period is at least about ninety days.
16. The program of claim 1, wherein said first regular basis is daily.
- 25 17. The program of claim 1, further comprising directing said subject to monitor said
subject's blood glucose levels during said first period.
18. The program of claim 17, further comprising directing said subject to monitor said post-
prandial blood glucose level at least weekly.
30
19. The program of claim 1, further comprising adjusting said program depending on said
comparison of said second HbA1c level to said first HbA1c level:

wherein if said second HbA1c level is appreciably improved from said first HbA1c level:

- i. providing, in a pharmaceutically acceptable excipient, a second composition comprising a reduced amount of said first bioavailable source of chromium and a reduced amount of said first bioavailable source of vanadium as compared to said amount of said first bioavailable source of chromium and said amount of said first bioavailable source of vanadium, respectively, in said first composition, wherein:
 - (a) said reduced amount of said first bioavailable source of chromium is determined by said second HbA1c level: for said subject having said second HbA1c level in the range of about 7 up to about 8%, said reduced amount of chromium from about 0.003 mg Cr or less/kg of said second body weight up to about 0.009 mg Cr/kg of said second body weight; for said subject having said second HbA1c level in the range of about 8 up to about 9%, said reduced amount of chromium from about 0.005 mg Cr/kg of said second body weight up to about 0.01 mg Cr/kg of said second body weight; for said subject having said second HbA1c level in the range of about 10 up to about 11%, said reduced amount of chromium from about 0.006 mg Cr/kg of said second body weight up to about 0.015 mg Cr/kg of said second body weight; or for said subject having said second HbA1c level in the range of at least about 11%, said reduced amount of chromium from about 0.007 mg Cr/kg of said second body weight up to about 0.04 mg Cr or more/kg of said second body weight; and,
 - (b) said reduced amount of said first bioavailable source of vanadium is determined by said second HbA1c level: for said subject having said second HbA1c level in the range of about 7 up to about 8%, said reduced amount of vanadium from about 0.05 mg V or less/kg of said second body weight up to about 0.4 mg V/kg of said second body weight; for said subject having said second HbA1c level in the range of about 8 up to about 9%, said reduced amount of vanadium from about 0.15 mg V/kg of said second body weight up to about 0.5 mg V/kg of said second body weight, for said subject having said

second HbA1c level in the range of about 10 up to about 11%, said reduced amount of vanadium from about 0.3 mg V/kg of said second body weight up to about 1.0 mg V/kg of said second body weight, or for said subject having said second HbA1c level in the range of at least about 11%, said reduced amount of vanadium from about 0.35 mg V/kg of said second body weight up to about 2.0 mg V or more/kg of said second body weight;

- ii. directing said subject to ingest said second composition on a second regular basis for a second period;
- iii. determining a third HbA1c level for said subject at about the end of said second period; and,
- iv. comparing said third HbA1c level to said second HbA1c level to determine any improvement in glucose metabolism by said subject during said second period;

wherein if said second HbA1c level is not appreciably improved from said first HbA1c level:

- i. directing said subject, according to one of the following, to: continue ingesting said first formulation on a second regular basis for a second period; provide, in a pharmaceutically acceptable excipient, a second composition, comprising: an increased amount of said first bioavailable source of chromium or an increased amount of said first bioavailable source of vanadium, or both, as compared to said amount of said first bioavailable source of chromium and said amount of said first bioavailable source of vanadium, respectively, in said first composition; or provide, in a pharmaceutically acceptable excipient, a second composition comprising: an amount of a second bioavailable source of chromium and an amount of a second bioavailable source of vanadium, wherein said second bioavailable source of chromium or said second bioavailable source of vanadium, or both, is different from said first bioavailable source of chromium or said first bioavailable source of vanadium, respectively, in said first composition;
- ii. directing said subject to ingest said first composition or said second

composition on a second regular basis for a second period;

iii. determining a third HbA1c level for said subject at about the end of said second period; and,

iv. comparing said third HbA1c level to said second HbA1c level to
5 determine any improvement in glucose metabolism by said subject during said second period.

20. The program of claim 19, wherein to be appreciably improved, said first HbA1c level must be more than about 15% greater than said second HbA1c level.

21. The program of claim 19, further comprising adjusting said program depending on said comparison of said third HbA1c level to said second HbA1c level.

22. The program of claim 1, further comprising reducing said amount of said first
15 bioavailable source of chromium or said amount of said first bioavailable source of vanadium, or both, if said second HbA1c level is appreciably improved as compared to said first HbA1c level.

23. The program of claim 22, wherein to be appreciably improved, said first HbA1c level
20 must be more than about 10% greater than said second HbA1c level.

24. The program of claim 22, wherein to be appreciably improved, said first HbA1c level must be more than about 20% greater than said second HbA1c level.

25. The program of claim 22, wherein to be appreciably improved, said first HbA1c level must be more than about 25% greater than said second HbA1c level.

26. A system to modulate blood glucose levels comprising:

a. manufacturing an orally ingestible medicament, comprising: a bioavailable source
30 of chromium in a complex and amount that delivers an effective dose of chromium, and a bioavailable source of vanadium in a complex and amount that delivers an effective dose of vanadium; and,

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- b. instructing a patient to ingest daily said medicament and to monitor said patient's blood glucose level,

wherein said dose of chromium is at least about 650 mcg chromium, and said dose of vanadium is at least about 10 mg vanadium, and wherein said blood glucose level is reduced by about twenty percent after ingesting said medicament for at least four weeks.

27. The system of claim 26, wherein said complex of chromium comprises chromium polynicotinate.

28. The system of claim 26, wherein said complex of vanadium comprises vanadyl and a counter-ion or ligand, or both.

29. The system of claim 26, wherein said dose of chromium is about 650 mcg chromium to about 1500 mcg chromium, and said dose of vanadium is about 10 mg to about 100 mg vanadium.

30. The system of claim 26, wherein said dose of vanadium is at least about 75 mg vanadium.

31. The system of claim 26, wherein said dose of chromium is at least about 1000 mcg chromium.

32. The system of claim 26, wherein said bioavailable source of chromium comprises chromium polynicotinate, and said bioavailable source of vanadium comprises vanadyl.

33. The system of claim 26, wherein said medicament further comprises a therapeutically effective amount of one or more of the following: alpha-lipoic acid, aspirin, a bioavailable source of magnesium, folic acid, vitamin E or vitamin A.

34. The system of claim 26, wherein said medicament further comprises a therapeutically effective amount of aspirin.

35. A program to assist subjects in losing weight, comprising:

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- a. manufacturing an orally ingestible medicament, comprising: a bioavailable source of chromium in a therapeutically effective amount, and a bioavailable source of vanadium in a therapeutically effective amount;
- b. determining a first body weight for a subject;
- 5 c. instructing a subject to ingest said medicament on a regular basis and to monitor said subject's weight; and,
- d. determining a second body weight after at least one month after ingestion of said medicament on a regular basis;

wherein said first body weight is at least about 5% more than said second body weight.

10 36. The program of claim 35, wherein said amount of said bioavailable source of chromium has a dose of chromium of at least about 650 mcg, and said amount of said bioavailable source of vanadium has a dose of vanadium of at least about 5 mg.

15 37. The program of claim 36, wherein said dose of vanadium is at least about 75 mg vanadium.

38. The program of claim 36, wherein said dose of chromium is at least about 1000 mcg chromium.

20 39. The program of claim 35, wherein said medicament further comprises a therapeutically effective amount of one or more of the following: alpha-lipoic acid, aspirin, a bioavailable source of magnesium, folic acid, vitamin E or vitamin A.

25 40. The program of claim 35, wherein said first body weight is at least about 10% more than said second body weight.

41. The program of claim 35, wherein said first body weight is at least about 15% more than said second body weight.

30 42. The program of claim 35, wherein said first body weight is at least about 25% more than said second body weight.

43. A program for reducing HbA1c level in a patient, comprising:
- a. providing a dietary composition consisting essentially of a therapeutically effective dose of chromium from a bioavailable source of chromium, and a therapeutically effective dose of vanadium from a bioavailable source of vanadium; and,
 - b. providing instructions to a patient, comprising:
 - i. directing said patient to determine a first HbA1c level for said patient;
 - ii. directing said patient to ingest said dietary composition for a period of at least ninety days;
 - iii. directing said patient to monitor said patient's blood glucose level during said period; and,
 - iv. directing said patient to determine a second HbA1c level for said patient after said period,
- wherein a ratio of said second HbA1c level to said first HbA1c level is about 0.90 or less.
44. The program of claim 43, wherein said dose of vanadium is at least about 75 mg vanadium.
45. The program of claim 43, wherein said dose of chromium is at least about 1000 mcg chromium.
46. The program of claim 43, wherein said ratio of said second HbA1c level to said first HbA1c level is about 0.85 or less.
47. The program of claim 43, wherein said ratio of said second HbA1c level to said first HbA1c level is about 0.80 or less.
48. The program of claim 43, wherein said ratio of said second HbA1c level to said first HbA1c level is about 0.75 or less.
49. The program of claim 43, wherein said ratio of said second HbA1c level to said first

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HbA1c level is about 0.66 or less.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/15585

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/555

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DOMINGO J.L. ET AL: "Tiron administration minimizes the toxicity of vanadate but not its insulin mimetic properties in diabetic rats." LIFE SCIENCES, (1992) 50/18 (1311-1317). , XP000901833 the whole document	26-34
Y	DOMINGO J.L. ET AL: "Administration of vanadyl sulfate by gavage does not normalize blood glucose levels in streptozotocin-induced diabetic rats." RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY, (1992) 75/3 (369-372). , XP000901829 abstract	26-34
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Gonzalez Ramon, N

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/15585

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No.
Y	CAM M.C. ET AL: "Long-term effectiveness of oral vanadyl sulphate in streptozotocin- diabetic rats." DIABETOLOGIA, (1993) 36/3 (218-224). , XP000901826 abstract ---	26-34
Y	GREGORY BOYD, S. ET AL: "Combined dietary chromium picolinate supplementation and an exercise program leads to a reduction of serum cholesterol and insulin in college-aged subjects" J. NUTR. BIOCHEM. (1998), 9(8), 471-475 , XP000901822 abstract ---	26-34
T	MONGOLD J.J. ET AL: "Toxicological aspects of vanadyl sulphate on diabetic rats: Effects on vanadium levels and pancreatic B-cell morphology." PHARMACOLOGY AND TOXICOLOGY, (1990) 67/3 (192-198). , XP000901818 abstract ---	26-34
Y,P	"Chromium picolinate for good health?" BIOLIFEPLUS.COM, 'Online! 16 October 1999 (1999-10-16), XP002135607 Retrieved from the Internet: <URL:www.biolifeplus.com/library/chromium.html> 'retrieved on 2000-04-05! the whole document ---	26-34
E	WO 00 12095 A (AMBI INC ;HARPE JON DE (US); PRICE FREDRIC D (US); SKLUTH LAUREN K) 9 March 2000 (2000-03-09) abstract ---	26-34
Y	AMOIKON, 3. K. ET AL: "Effect of chromium tripicolinate on growth, glucose tolerance, insulin sensitivity, plasma metabolites, and growth hormone in pigs" J. ANIM. SCI. (1995), 73(4), 1123-30 , XP000901969 abstract ---	26-34
A	SPEARS, J. W. (1): "Reevaluation of the metabolic essentiality of the minerals: Review." ASIAN-AUSTRALASIAN JOURNAL OF ANIMAL SCIENCES, (SEPT., 1999) VOL. 12, NO. 6, PP. 1002-1008. , XP000901962 abstract page 1004 -page 1006 --- -/--	26-34

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 99/15585

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	US 5 980 905 A (DE LA HARPE JON ET AL) 9 November 1999 (1999-11-09) abstract ----	26-34
E	US 5 962 030 A (FINE STUART A) 5 October 1999 (1999-10-05) column 10; claims 1,15,26,28,44 ----	26-34
X	WO 98 42211 A (PROGRESSIVE RESEARCH LABS) 1 October 1998 (1998-10-01) abstract claims 1-4,16,24-26; example 1 -----	26-34

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 15585

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-25, 35-49
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT- Diagnostic method practised on the human or animal body
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0012095 A	09-03-2000	US 5905075 A US 5980905 A FR 2782640 A	18-05-1999 09-11-1999 03-03-2000
US 5980905 A	09-11-1999	US 5905075 A WO 0012095 A FR 2782640 A	18-05-1999 09-03-2000 03-03-2000
US 5962030 A	05-10-1999	NONE	
WO 9842211 A	01-10-1998	US 5730988 A AU 6768998 A GB 2338187 A	24-03-1998 20-10-1998 15-12-1999