Review Article and Clinical Experience:
THE ROLES OF MICRONUTRIENTS IN THE TREATMENT OF DIABETES MELLITUS
(Focus on Chromium and Specific Nutrients)

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ABSTRACT

It is estimated that the glucose disposal of whole body insulin sensitivity reflected by the muscles, liver, and adipose tissues are approximately 60%, 30%, and 10%, respectively. However, the adipose tissue may play a pivotal role in the induction of Insulin Resistance (IR) in the muscles and the liver. Marked impairments in insulin’s intracellular signaling cascades are present in fat cells of Type-2 Diabetes Mellitus (T2DM), including: 1. reduced IRS-gene and protein expression, 2. reduced IRTK activity, 3. impaired insulin-stimulated PI3-kinase activity, 4. impaired PKB / Akt activity, and 5. reduced GLUT 4 expression. These impairments are also found in some (~30%) normoglycemic individuals with genetic predisposition for T2DM. The Syndrome-X was firstly coined by Reaven in 1995 and then to be provided in 1999 by the name: the Metabolic Syndrome-X. This Syndrome represents a “Cluster” of metabolic disorders and cardiovascular risk factors which includes: 1. Insulin Resistance / Hyperinsulinemia, 2. Central Obesity, 3. Glucose Intolerance, 4. Atherogenic Dyslipidemia (↑ TG, ↓ HDL-Chol., ↑ Apo-B, ↑ Small Dense LDL), 5. Hypertension, 6. Prothrombotic State (↑ PAI-1, ↑ F-VII, ↑ Fibrinogen), 7. Endothelial Dysfunction, and 8. Hyperuricemia. Such a “Cluster” may lead to the development of T2DM and Coronary Heart Disease (CHD). An excessive Free Radicals (FR) production (caused by the antioxidant’s levels to fall below the normal in T2DM) is thought to play significant roles in the development of Diabetic Vascular Complications (DVs). Several antioxidants such as Raxofelast (600 mg bid), Thiotic Acid (Alpha Lipoic Acid), Vit.C, Vit.E, Zn have been reported to be successful to overcome Oxidative Stress. Hence, it is rationale to deduce that antioxidant micronutrients would be useful in patients with T2DM. Clinical evidences indicate the benefit effects of selected minerals, trace elements, and vitamins such as: Cr, Mg, Zn, Cu, (and others: Mn, I, Se, Fe), and vitamins (B1, B6, B12, Folic Acid, Niacin, Biotin, C, E). Such beneficial effects include: the improvement of insulin secretion and peripheral sensitivity, carbohydrate metabolism, and lipid profiles, even the protective effect against tissue damage caused by lipid peroxidation. It can be summarized from several studies that supplemental Chromium (Cr), 200ug until 1000 ug per day to patients with T2DM for 1-10 months showed beneficial effect; increased insulin binding to cells, insulin receptor number, and activated Insulin Receptor Tyrosine Kinase = IRTK = IRTK (8-fold) leading to increased insulin sensitivity. Chromium also inhibits Phospho Tyrosine Phosphates (PTP-IB) that inactivates the insulin receptor. The activation of IRTK by Cr and the inhibition of insulin receptor tyrosine phosphatase lead to the increased phosphorylation of the insulin receptor and to the increased insulin sensitivity. In a double blind, placebo controlled study (with T2DM patients), Cr was shown to improve glucose, insulin, cholesterol blood levels and AIC in a dose-dependent manner (200-1000 ug/day) after 4 months.

A Cluster of determinant factors for the risk of Cardiovascular Diseases called Syndrome-37 will be listed. Conclusion: Insulin resistance and compensatory hyperinsulinemia lead to the development of the Metabolic Syndrome-X. Oxidative Stress in Diabetes Mellitus caused the increased risk of atherosclerosis. Clinical evidences show beneficial effects of micronutrients especially in insulin secretion and peripheral sensitivity, glucose homeostasis, and lipid profiles, even in neutralizing free radicals. Hence, micronutrients (esp. Chromium) have potential therapeutical benefits for patients with Diabetes Mellitus.

Keywords: micronutrients, Diabetes Mellitus, chromium

INTRODUCTION

Estimation of whole-body insulin sensitivity and action with the euglycemic clamp technique is mainly a reflection of the glucose disposal by the muscles (~60%). The adipose tissues only account for ~10% of the insulin-stimulated whole body glucose uptake and liver for ~30% (De Fronzo et al 1992). Insulin Resistance (IR) followed by compensatory hyperinsulinemia may lead to the development of Insulin Resistance Syndrome or SYNDROME-X (firstly coined by Reaven in 1995) which represents a cluster of metabolic disorders and cardiovascular risk factors. In 1999, Reaven renamed these abnormalities as the Metabolic Syndrome – X which more complete than the previous one and consists of 8 components as mentioned below.

1. Insulin Resistance / Hyperinsulinemia
2. Central Obesity
3. Glucose Intolerance / Diabetes Mellitus
4. Atherogenic Dyslipidemia
a. Increase in Plasma Triglyceride
b. Decrease in Plasma HDL-Cholesterol
c. Increase in Apoprotein-B
d. Increase in Small Dense LDL (Type B pattern)

5. Hypertension

6. Prothrombotic State
   a. Increasing in PAI-1
   b. Increase in F-VII
   c. Increase in Plasma Fibrinogen

7. Endothelial Dysfunction
   a. Increase in Urinary Albumin Excretion

8. Hyperuricemia

Hence, abnormalities in insulin secretion and action, in glucose homeostasis, and in lipid profile are closely correlated with uncontrolled diabetic patients. Moreover, increased levels of oxidative stress and other risk factors may underlie the increased risk of cardiovascular disease in patients with poorly controlled diabetes. Recent evidences indicated that specific trace elements, minerals, and vitamins showed beneficial effects (improvement of insulin secretion and action, glucose homeostasis, lipid profiles, and also as antioxidants) in diabetic patients. The essential micronutrients, especially Chromium (Cr), involve in the metabolism of glucose, insulin, and blood lipids. The aim of this paper is to give basic information to the participants and readers about the Metabolic Syndrome-X and the roles of specific micronutrients (esp. Chromium) in the treatment of patients with Diabetes Mellitus and its associated complications. Syndrome-37 (Tjokroprawiro, 2003) which represents a cluster of determinant factors of cardiovascular diseases will be presented (Figure 1).

THE METABOLIC SYNDROME – X
(Focus on Insulin Action and Insulin Resistance)

The 8-components of this syndrome have been listed. The Oxidative Stress in Diabetes Mellitus (DM) will be shortly described (Tjokroprawiro 2001). A particular individual may have as few as 2 or 3 components of the Syndrome to as many as all of the 8-components. This Syndrome can be recognized long before it has any clinical manifestations. Numerous studies have shown that the Metabolic Syndrome precedes the development of Type-2 Diabetes Mellitus (T2DM) by many years depends on the life style of the individuals. In the San Antonio Heart Study (Stern et al 1993), it was associated as much as a 13-fold increased risk for the development of T2DM. Similarly, it precedes the development of Coronary Heart Disease (CHD) and in several epidemiologic studies conferred a 2 to 3 –fold risk for CHD. Insulin-Receptor (IR) signaling involves two major pathways (Roith et al 2001):

1. The P13-K Pathway (Phosphatidyl Inositol 3,4,5 Phosphate)
2. The MAPK Pathway (Mitogen-Activated Protein Kinase)

It should not be forgotten that each pathway could (under certain circumstances) activate the other. Thus, PKB / Akt may activate Raf Kinase, and conversely. Thus, the two pathways can be schematically drawn below.

The MAPK Pathway (Atherogenic = “Villain Pathway”): IR → SHS → Grb2 → m SOS → Ras → Raf → MEK → MAPK → Gene Expression / Mitogenic (Atherogenic).

The P13-K Pathway (Atheroprotective = “Hero Pathway”): IR → IRS proteins → divided into 2 pathways:

1. IR → Grb2 → m SOS → Ras → Raf


Initially, the activated IR will bind SHC and IRS molecules and these interact with downstream substrates. The P13-K Pathway leads to a large variety of biological actions after IR activation. The aggravated insulin resistance of T2DM is primarily of a postreceptor nature (Caro et al 1987). IR Tyr Kinase (IRTK) activity in patients could be inhibited because of elevation in Tyr phosphatase activity (Kasari et al 1994) or enhanced Ser/Thr phosphorylation of the receptor that impairs its Tyr kinase activity (Haring 1991, Dunaif et al 1995). Ser/Thr phosphorylation of the IR occurs in response to the treatment of cells with insulin (Tavare et al 1991), or with activators of PKC or the cAMP-dependent protein kinase (Stadtmauer et al 1986, Takayama et al 1988). Accordingly, downstream signaling cascade would be decreased in proportion to the defect in IRTK activity; apparently, however, when compared with the reductions in Tyr phosphorylation of the IR and IRS-1, P13-K is more severely reduced in T2DM (Goodyear et al 1995).

There are many mechanisms by which hyperglycemia may increase the production of free radicals = FRs (Tjokroprawiro 2001). Glucose autooxidation has a capability to yield oxidizing intermediates, such as O2, OH, and H2O2 (Hydrogen Peroxide). These substances can damage lipids and proteins through cross-linking and fragmentation. Free radicals may accelerate the generation of AGEs, in turn, supply, more FRs. Retina, Lens, Kidney, and Peripheral Nerves are tissues where glucose uptake is independent of insulin. Hence, all those tissue are the most prevalent sites of Diabetic Vascular Complications (DVCs).
In conclusion, Oxidative Stress (OS) in uncontrolled DM will be increased; OS is one of the major mechanisms of hyperglycemic tissue damage and acts as a key role in the development of DVCs.

THE ROLES OF CHROMIUM IN THE TREATMENT OF DIABETES

The dominating factor in the raped risk in the incidence of DM is likely to be dietary factors. Increase intakes of simple sugars and fats, which are known to decrease insulin sensitivity, are likely causes of the increasing incidence of DM. Of micro-nutrients, the one most limiting the diet and shown to have the largest effects on the signs of DM in humans is Chromium (Anderson 1998).

Chromium (Cr) was the first reported to play a role in controlling blood glucose in the late fifties and several recent studies have documented its effects in people with glucose intolerance and DM. Improved fasting and glucose tolerance with lower or similar levels of circulating insulin have been reported in several studies involving Cr supplementation of people with varying degrees of glucose intolerance.

In a follow-up survey, the fasting and postprandial glucose, and diabetic symptoms of 833 patients with T2DM were monitored for up to 10 months following Cr supplementation 500 ug/day Cr as Chromium picolinate (Cheng et al 1999). All subject were on hypoglycemic medication and/or insulin. Fasting and post prandial glucose improved in > 90% of the subjects and similar improvement occurred after 1-10 months. Symptoms of DM including fatigue decreased up to 12% (thus, 88% of patients are successful). No adverse reactions were observed. These data confirm the safety and beneficial effects of supplemental Chromium.

Ravina et al (1999) in the recent study demonstrated that supplemental Cr 200 ug 3 times daily (as Chromium picolinate) was useful in the control of steroid-induced diabetic patients. Most of patient (94%) with steroid-induced DM could be controlled by supplemental Cr, 200 ug of Cr as Cr picolinate, 3 times daily. Prior to the initiation of supplemental Cr, hypoglycemic agents were also reduced 50%. Following two weeks of 600 ug per day of supplemental Cr, daily Cr intake was reduced to 200 ug. Ten percent (10%) of the 50 patients were able to stop all forms of hypoglycemic agents, and good glycemic control could be maintained by taking 200 ug of Chromium daily.

Over production of insulin in the Chromium-deficient Rats was demonstrated by Striffler et al (1999). The hyperresponsiveness in this experimental Rats is likely the result of decreased peripheral tissue sensitivity of insulin. In a recent double-blind, placebo-controlled study involving 180 patients with T2DM, supplemental Cr (Cr picolinate 1000 ug/day compared with 200 ug/day) was shown to improve fasting glucose, post prandial glucose, insulin, AIC, and cholesterol (Anderson et al 1997). The two-hour blood glucose values were significantly lower after 2 months in the group receiving 1000 ug/day supplemental Cr, and after 4 months were lower in both groups receiving supplemental Cr. Insulin was significantly lower in both Cr group after two and four months. Plasma total cholesterol also decreased after consuming 1000 ug of Cr, per day for 4 months. AIC was 8.5 ± 0.2% in the placebo group, 7.5 ± 0.2% in the 200 ug group and 6.6 ± 0.1% in the group receiving 1000 ug of Cr/day for four months.

In a follow-up study involving more than 800 patients with T2DM, blood glucose and symptoms of DM including excessive thirst, urination and fatigue improved over 80% of the patients (Cheng et al 1999). Improvement in glucose, insulin and related variables in response to Cr normally occur within a few weeks or less. However, improvement in blood lipids may take longer.

In the study of Abraham et al (1992) involving supplement (250 ug per day of Cr as Cr Chloride) of 25 patients with DM and atherosclerotic diseases, improvement in HDL and Triglyceride took more than 6 months. A limited number of studies (Shermann et al 1968, Rabinowitz et al 1983) reported no beneficial effects of supplemental Cr which is usually not adequate for patients with DM, especially if is in a form with low absorption.

Pregnancy is a state of insulin resistance and if a women’s pancreas can not increase insulin production and/or efficiency to compensate for the increasing needs throughout pregnancy, gestational diabetes (GDM) occurs. Jovanovic et al (1999) in the study of 30 women with GDM (20-24 gestational weeks) with supplemental Cr-picolinate of 0.4,8 ug Cr/Kg BW for 8 weeks concluded that:

1. Chromium supplementation in GDM improved glucose intolerance and lowered hyperglycemia
2. Chromium effects in the group receiving 8 ug Cr/Kg BW were greater than those receiving 4 ug/Kg BW
3. Chromium supplementation may be as an adjunctive therapy for patients with GDM when dietary regimens are not sufficient to achieve good glycemic control.
Beneficial effect of supplemental Cr on patients receiving TPN (Total Parenteral Nutrition) have been reported by Freund et al (1979), and Brown (1986). Chromium is now routinely added to TPN solutions and Cr recommendations for TPN patients have been reviewed (Anderson 1995). Peripheral neuropathy and fractional glucose clearance were improved after supplementation Cr (250 ug/day Chromium Chlorate).

POSSIBLE MECHANISMS OF ACTION OF CHROMIUM

Possible mechanisms of Cr in the control of blood glucose are due to the improvements of receptor and post receptor actions.

1. Supplemental Cr leads to increased insulin binding to cells due to increased insulin receptor number (Braithwaite et al 1998).
2. Improved glucose utilization and sensitivity of Beta-Cell have also been demonstrated. Chromium activates IRTK (Insulin Receptor Tyrosine Kinase) 8-fold in the presence of insulin but does not in the absence of insulin (Davis et al 1997).
3. Chromium inhibits Phospho Tyrosine Phosphatase-1 (PTP-1), a rat homolog of a Tyrosine Phosphatase (PTP-IB) that inactivates the insulin receptor (IR).

Conclusions: The increased affinity to IR, the increased IR-number, the activation of IRTK, and the inhibition of IR Tyrosine Phosphatase, all of these lead to the increased insulin sensitivity. The Reference Dose established by the US Environmental Protection Agency for Cr is 350-times the upper limit of the Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 3.85 mmol (200 ug/day). The Reference Dose (R/D) is defined as ‘an estimate of a daily exposure to the human population, including sensitive subgroups, that is likely to be without an appreciable risk of deleterious effect over a lifetime” (Mertz et al 1994). Anderson et al (1997) demonstrated no evidence of toxicity or toxic effects in any of the human studies involving Chromium Supplementation.

THE ROLES OF OTHER SPECIFIC NUTRIENTS IN DIABETIC PATIENTS (VITABIOTICS DRUG INFORMATION, 2001)

Magnesium

1. Involved in insulin secretion and glucose homeostasis
2. Hypomagnesemia due to increased urinary excretion in diabetics is associated with:
   a. Reduced insulin secretion or increased insulin resistance
   b. Reduced erythrocyte Magnesium levels, oxygen uptake and work capacity
   c. Reduced PTH secretion, upset in calcium homeostasis, and osteopenia
   d. Increased retinopathy, hypertension, abnormalities of lipid profile, and IHD.

In extensive dietary surveys Magnesium intake has been found to be below the RDA in 75% of the population worldwide. Moreover, hyperglycemia has been shown to accelerate Magnesium turnover in cells and total Magnesium deficiency. Reduced intracellular free magnesium levels affect over 300 enzymatic processes and all ATP-related reactions. Suppemental Magnesium improves the energy level, insulin responsiveness and glycemic control.

Zinc

1. Directly participates in the production, storage and release of insulin.
2. Protects against tissue damage caused by lipid peroxidation.
3. Hyperglycemia induces hyperzincuria and Zinc deficiency, which are related to:
   a. slow healing of ulcers
   b. neuro-sensory changes
   c. impaired immune function
   d. low testosterone levels.

Copper, Manganese, Iron

1. Their status is very often “marginal” (or sub-optimal) in diabetics.
2. Deficiency contributes to
   a. impairment of glucose tolerance,
   b. elevated serum total cholesterol, and
   c. increased serum triglycerides.

Anti-Oxidants (Selenium, Vit. C, Vit. E, Vit. A)

Patients with Type 2 Diabetes Mellitus (T2DM) and essential hypertension have decreased anti-oxidant capacity, increased production of free radicals, increased oxidative stress, increased oxidation of cell components and HDL-Cholesterol, and increased risk of atherosclerosis. Current clinical research data shows that anti-oxidants improve the free radicals defense system potential, and have beneficial effects in improving glucose transport and insulin sensitivity. It has been also shown that inhibition of oxidation process by co-adjuvant anti-oxidant therapy helps prevent, or at least delay, the onset and/or progression of DVCs. In addition, long term / low-dose administration with anti-oxidant “cocktails” (as opposed to large-dose
administration of a single anti-oxidant) has been shown to
a. inhibit haemoglobin glycation,
b. lower serum cholesterol levels in hypercholesterolemic diabetics,
c. prevent micro-angiopathies and atherosclerosis, and
d. protect against tissue damage by peroxides from lipid metabolism and show down the progress of atherosclerosis.

B-Vitamins
Deficiencies of Thiamin, Niacin, vitamin B6 and vitamin B12 are specifically associated with glucose intolerance and T2DM.

Folic Acid, Vit. B6, Vit. B12
1. Deficiencies of Folic acid, vitamin B6 and vitamin B12 result in elevated plasma Homocysteine (tHcy) levels which are serious risk factors for CHD, athero-thrombotic stroke and peripheral vascular disease.
2. Moderate supplementation effectively lowers elevated tHcy levels.
3. Folate supplementation also enhances lipoprotein lipase activity, which results in decreased plasma levels of Triglycerides, VLDL-Cholesterol and LDL-Cholesterol, and in higher activity of HDL-Cholesterol.

Biotin
1. Biotin deficiency, inactivity or unavailability affects the nervous system metabolism, leading to peripheral neuropathy.
2. Enhanced Biotin intake is associated with lower post-parandial glucose level, improved glucose tolerance and decreased insulin resistance.
SYNDROME-37: A CLUSTER OF DETERMINANT COMPONENTS OF ENDOTHELIAL FUNCTION

SYNDROME-37 : GIGULOCHIPS-SAF3ARIL-PAIC2-GEL-TH-CuFITEGI

Based on House to House Survey in Indonesia, it was reported that Atherosclerotic Cardiovascular Diseases (ASCVD) was claimed as the 11th, the 3rd, the 2nd, and the 1st killer in Indonesia by the years 1972, 1986, 1992, and 1993-1995, respectively. Syndrome-11 (1992 & 1993), Syndrome-20 (1994), Syndrome-23 (1995), Syndrome-26 (1996), Syndrome-27 (1996), Syndrome-29 (1997), Syndrome-30 (1998), Syndrome-32 (1999), Syndrome-33 (2000), Syndrome-34 (2001), Syndrome-36 (2002), and finally Syndrome-37 (2003) have been coined consecutively by Tjokroprawiro since 1992, in which the latest described about 37 determinant factors that are responsible for the quality of Endothelial Cell and Blood Vessels, hence, responsible for the quality of Life. SYNDROME-37 (GIGULOCHIPS-SAF3ARIL-PAIC2-GEL-TH-CuFITEGI) can be used as ASCVD-check list, and shows the image of the quality of blood vessels of patients. This syndrome stands for: Genetic, Insulin Resistance, Glucose Intolerance, Uric Acid, Lipids, Obesity, Cigarette, Hypertension, Inactivity, Platelet Dysfunction, Stress-Sex, Age, Fibrinogen, F-VIIIc & F-VII, Free Radicals, Alcohol Abuse, Race, Inhibitors (Growth Inhibitors), Left Ventricle Hypertrophy, PAF, Androgen, Interleukines, Cortisol, Catecholamine, Growth Hormone, Estrogen, Leptin, TNF-α, Homo-cysteinemia, Cu, Fe, Inflammation, TGF-β, Endothelin, Gamma-GT and Infection.

CONCLUSION: Physically, The Quality of Life completely depends on The Quality of the Endothelial Cells. By controlling factors described in Syndrome-37, lower prevalences of ASCVD may pursue. Hence, it is hoped that the prevalence of ASCVDs by the year 2003 can be pushed back towards the figure as reported in the year 1972.

THE QUALITY OF ENDOTHELIAL CELLS COMPLETELY DEPEND ON THE QUALITY OF SYNDROME-37
THE QUALITY OF LIFE “IS IN LINE WITH” THE QUALITY OF ENDOTHELIAL CELLS

FIGURE-1. SYNDROME-37: A Cluster of 37 Components (Tjokroprawiro 2003)
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